THE STATUS AND IMPLICATIONS OF ONCOGENE RESEARCH

HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

COMMITTEE ON
SCIENCE AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

NINETY-EIGHTH CONGRESS

SECOND SESSION

JUNE 6, 1984

[No. 114]

Printed for the use of the
Committee on Science and Technology

38-261 O

U.S. GOVERNMENT PRINTING OFFICE
WASHINGTON : 1984

H701-31

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THE STATUS AND IMPLICATIONS OF ONCOGENE RESEARCH

WEDNESDAY, JUNE 6, 1984

House of Representatives,
Committee on Science and Technology,
Subcommittee on Investigations and Oversight,
Washington, DC.

The subcommittee met, pursuant to call, at 9:40 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee) presiding.

Mr. **Gore**. The hearing will come to order.

I'd like to welcome all of our witnesses and guests and get this hearing under way. I have a brief opening statement, then I'll recognize my colleague and we'll go to the first panel.

Ten years ago, the word "oncogene" was unknown to most scientists. Today, oncogenes, that is, genes which are intimately involved in the onset and initiation of cancer, are regularly the subject of feature articles in many of our leading papers and have been the subject of lead articles in popular magazines such as the Reader's Digest.

Also, reports of new drugs, methotrexate for astrocytoma, a form of brain cancer, interferon for a variety of cancers, and reports of new types of therapy, such as the development of highly specific monoclonal antibodies used to successfully treat an advance case of lymph gland cancer and of the creation of a specific bullet to directly attack tumors, eliminating the need for much less direct chemotherapy or radiation treatments, all of these have become commonplace reports.

These developments, all taking place within the past few years, are the result of a synthesis of research efforts in genetic engineering and oncology. Advances in molecular biology, such as the ability to splice genes, have provided techniques which permit researchers to view at the molecular level the onset of tumors.

It is these studies which have created the excitement that now exists in oncology research laboratories in the United States and throughout the world. As more basic information becomes available, the rate of progress in terms of attempted and successful applications increases.

The intense public interest in cancer research is a reflection of everyone's hope that this research will result in prevention and treatment procedures for cancer which will reduce its standing as the only major cause of death in the United States, which has risen continuously for nearly 80 years.

While progress has been made in the treatment and cure of cancer, 450,000 people still die each year of cancer in the United States. There are 870,000 new cases reported each year.

The heightened public awareness of developments in cancer research has resulted in a shift in public opinion. Between 1979 and 1981, the percent of the public believing that a cure for cancer will be readily available within 25 years rose from 48 percent to 61 percent. Seventy-four percent of those without a college education held this view, all of which leads to an impressive support at the 82 percent level for continued advances in biological and medical science.

I am sure that today, with the many reports about progress in cancer research, more people than ever believe that we are even closer to success in curing cancer.

One of the witnesses whose statement I read on the airplane this morning expressed a sentiment which I would like to also express at the beginning of this hearing, and that is to caution families and patients who are dealing with cancer in later stages against any false hope as a result of the work that is being reported on at these hearings by the witnesses today. Although these developments are exciting, it will be quite a few years before successful applications are readily available, and the burden that cancer patients and their families have to bear should not be increased by any undue optimism or a false perspective on these new discoveries. They are, nonetheless, exciting.

The overall objective of this hearing is to determine how realistic the hope is, and how far we are from practical results. To answer this question, we have some of the leading experts in the country to discuss the science and the prospects for the future.

Our specific objectives are: First, to find out how we reached our current state of knowledge. What prompted the initial and continued interest in and funding of oncogene research, and what part of the overall cancer research effort this represents?

Second, we want to find out what oncogenes are and what their significance is in terms of cancer treatment and diagnosis and because of the potential for a better understanding of the process of onset and development of the disease; and third, we want to obtain information to better understand the practical applications of research findings and to determine a realistic timeframe for general patient treatment.

The first panel will present the viewpoint of two leading organizations in cancer research. We are fortunate to have with us representatives from the National Cancer Institute and the American Cancer Society, who will set the stage by discussing why and how we got to where we are.

At the research level, we will hear on the second panel from academic and industrial researchers who will explain to us in laymen's terms, I've been assured, what is going on in the research laboratory today, what the near future holds, and where we are headed over the long haul. I'm sure we will have an outstanding presentation, which will enable us to understand the testimony of the third panel, which will focus on application of research findings and the selection of research direction in an industrial setting.

In summary, when this hearing ends, I hope that we will be better able to understand what is meant when we see newspaper column headings like, "Scientists May Have Found Missing Link in Cause of Cancer," and "Research is Targeting Seeds of Cancer."

Before we go to the first panel, I am pleased to recognize the ranking minority member of the subcommittee, Mr. Skeen.

Mr. **Skeen**. Thank you very much, Mr. Chairman, and I also want to welcome the witnesses and those who are here today and interested in this particular topic.

For far too long, the word "cancer" to most lay people meant death. No relief, no alternative, but it meant death. And I think that that was a horrible prospect for most of us in the United States.

I hazard a guess that there is not a person in this room that has not been touched by this invidious disease at some time or another along their lifespan or will have some familiarity with it.

With this kind of panel and the kind of research that's going on is hope. And I think that is the most important thing. Those of us who have studied this disease, been interested in it, are amazed at the progress we have made and I appreciate the caveat that you gave in saying that with the advancement of the research and the techniques that we have now in treating cancer, that we don't want to become too hopeful, but let's look at what's happened over a span of just a few years.

Two decades have taken the word "cancer" as a hopeless word in our vocabulary and made it one that is a little more hopeful because the percentages are so much better today than they were before.

So I want to express my appreciation for the kind of research that you people do and the kind of interest that you have, as we have, as a committee here. I commend you, Mr. Chairman, for having this hearing this morning.

So I think it is time that we got on with that hearing and thank you very much for the opportunity to welcome them here.

Mr. **Gore**. Well, thank you, and we're going to get under way. Let me say that for those who have our witness list, we have one substitution. Dr. Rosenberg is not on the formal list, but he had earlier been a witness and canceled yesterday and we have a substitute. We are pleased to have Stephen S. Turner, president of Oncor, Inc., and he will help us with the commercial perspective at the end of the hearing.

Let me welcome now our first panel which consists of Dr. Peter J. Fischinger, Associate Director of the National Institutes of Health, out at the National Cancer Institute in Bethesda; and Dr. William Feller, president-elect of the American Cancer Society, based here in Washington.

We're delighted to have both of you join us and get us off to a good start. I'd like to ask you to keep your formal presentations somewhat brief, if you can, and without objection, we will put your entire prepared statements into the record and we look forward to hearing from you.

We will begin with you, Dr. Peter Fischinger.

STATEMENTS OF DR. PETER J. FISCHINGER, ASSOCIATE DIRECTOR, NATIONAL INSTITUTES OF HEALTH, NATIONAL CANCER INSTITUTE, BETHESDA, MD; AND WILLIAM FELLER, PRESIDENT-ELECT, AMERICAN CANCER SOCIETY, WASHINGTON, DC

Dr. FISCHINGER. Thank you, Mr. Chairman, and members of the subcommittee.

Mr. GORE. If you could slide that microphone up there closer to you.

Dr. FISCHINGER. Right.

Mr. GORE. All right.

Dr. FISCHINGER. On behalf of the National Cancer Institute and its Director, Dr. Vincent T. DeVita, we really welcome the opportunity to present a status report on oncogene research and to address the direction and opportunities that these findings may have on diagnosis, treatment, and eventual prevention of human cancer.

You will hear a fascinating story, which is a culmination of about 10 years of research in the area of virus-induced cancer. We have used the tumor-inducing viruses as a tool to pry open a window on the very secrets of life. We now know that these secrets lie in the genes themselves, and we know that about 2 dozen of these genes can now be identified, isolated, and studied in great detail and we know they're involved in the causation of cancer.

These genes have been termed "oncogenes," from the Greek word, "oncos," meaning tumor. We know that we all have these genes in our warehouse of our DNA. Under normal conditions, these genes do code for important cellular functions. But now we also know how they go wrong.

I think the topic for today is precisely a definition as what has been happening. The subject is, of course, very complex and we will try to translate these in some very basic terms.

We also recognize that science is this area is at a very important point because we will discuss the practical applications and the modern biotechnologies in the context of what's happening.

We have experienced a biological revolution and now we feel we are on the threshold of actually bringing some of this technology to the bedside of the cancer patient. I think one of the very interesting developments has been that in the past, people have studied virus-induced cancers and chemicals that induce cancer and thought that these were different disciplines.

I think today, the status of oncogene research has actually unified these concepts and we are now looking at a very kind of unified theory as to how cancer is caused. In other words, we are really getting down to the basic causes of how cancer comes about.

In terms of trying to better the mortality from cancer that has been alluded to, the National Cancer Institute, of course, has predicted that by the year 2000, the cancer mortality in this country can be cut in half, and that is only by the application of the state-of-the-art treatment and by using nominal appropriate preventive measures.

What we have not counted in is the fact that this wealth of information that we're seeing in the area of oncogenes will probably increase these numbers. We are really expecting some payoffs in the near future.

Now, obviously, I think the scientific areas will be discussed in great detail by my colleagues and I will, therefore, in terms of brevity, not go into actually how the concepts got to be, how oncogenes act, the fact that they do have a normal function in cells, the fact they can move around in cells fairly well, and the fact that these oncogenes can actually increase in number within cells and make that malignant cell behave even worse than before.

So I think this is something that will require good, long, studious discussion and I think it will be very useful.

From the perspective of the National Cancer Institute, we have to say that we have been in the very forefront of research in this area. We have had an intensive virus cancer program from which these concepts actually developed, and we're talking about 10 to 12 years of very intensive research.

I would like to say that scientists at the National Cancer Institute had both predicted the way these genes are going to look like, and when the first findings were reported in 1976, two out of the three laboratories that reported the existence of oncogenes were actually at the National Cancer Institute.

In 1980, two laboratories at the National Cancer Institute were the first to use recombinant DNA technology and get these genes actually into bacteria and grow them. Two years ago, the Institute has decided that a strong impetus and stress is necessary in this area and we have put the stress into our research in the Frederick Cancer research facility in Frederick, MD.

I think one of the most exciting things that we're doing right now we're going to try to bring the state and the art of the science to a higher level by introducing the concept of supercomputing that may further advance us in this area, and we're also thinking of having a first application of a supercomputer to biomedicine and specifically in this area of oncogenes.

Let me next address the possible opportunities in the diagnosis and treatment of cancer. You are absolutely correct, Mr. Chairman, that these findings are at present research findings. However, we do see definitive directions in which some of these problems can be moved.

For example, we know for a fact that in cancer, as well as in some of the very important genetic diseases, we can begin to disagnose on a molecular level, with great certainty, the carriers of serious genetic diseases. These findings have only come up in the last year or so.

In counterpart, we also know that certain cancers will have genetic changes, that we first see in a level of chromosomes that carries these genes. Now we can begin, we think, to construct probes that will be highly specific for certain tumors. For example, in childhood, we have tumors of the eye called retinoblastoma and tumors of the kidney called Wilm's tumor. We know, for example, that these tumors will have specific chromosomal and molecular changes and oncogenes are functioning somewhere in the vicinity. What we would like to do, for example, is to be able also to devise certain diagnostic kinds of tests where we could start seeing whether the patient is at high risk or whether the patient's parents may be actually carriers of the genetic potential that can eventually result in tumors, not only in childhood, but also in terms of certain adult tumors.

We know, for example, that there is a great predisposition toward cancer that happens to be genetics. Even based on recent news, we know that colons in the large intestine will have a possibility of turning into cancer and we know that there are genetic diseases in families where people might have literally hundreds of such polyps in a colon and we know that with great certainty one of these polyps can go bad.

We think that it would be of great benefit if we could begin to see when such a polyp is going to turn into a malignant tumor. For example, we do know in terms of transforming of oncogenes that if you take such a tumor out, you will know that there is an activated oncogene in it. We also know that the normal, let's say, organs from that patient, will not have activated oncogenes. However, we would be very happy if we could be able to tell as to what is happening in advance of the actual tumor.

Another very major example that I would like to bring up is the fact that one of the most obvious causes for a very lethal tumor in men that kills, for example, 100,000 people every year, which is lung cancer. A great majority of this lung cancer can simply be prevented by cessation of tobacco smoking.

However, the whole fact is confounded by the fact that most of us know people who have smoked heavily all their lives who seem to be well, and we know that among even these very heavy smokers, only about 10 to 20 percent of them will actually come down with tumors. So, the idea is we are seeing literally tens of thousands of young men and women dying of this disease and could we in some way anticipate in trying to identify those individuals that really are at highest risk. To me, this would be a very tremendous advantage.

OK. Another area that we would like to address very briefly is the possibility of treatment. What can we actually do today, and I think you mentioned the questions of some of the advanced technologies in the area of immunology such as monoclonal antibodies. OK, what we really want to do is, since we know that an oncogene will have a product which is in some way abnormal, to see whether or not we can make highly specific monoclonal antibodies that recognize the abnormal product while not recognizing the normal product, because what we can do then, we can really zero in with such a monoclonal antibody and one can liken it to a missile that can hone in on the tumor cell and the next thing we can do, we can arm this missile. We can put a radioactive tracer on it and try to find exactly where small numbers of tumor cells are localized in the body.

Alternatively, we can also put a different radioactive molecule on this missile and can hone it in on the tumor cell and the tumor cell will be killed.

Mr. **Gore**. You are talking about a smart antibody.

Dr. **Fischinger**. That's exactly right, a smart antibody.

As a matter of fact, I would like to stress that these things are being done on an experimental basis today at the clinical center, and a number of other centers in the country. We are getting there.

Now, basically, I think I would like to go very briefly in terms of how we got to be and what the history of our funding has been in this area. We would say that the success of oncogene research, can be traced directly to support of virus cancer research, which began to expand very significantly in 1970. In that year, we spent about $21 million toward this effort.

The pace of this research increased tremendously over the next few years, so that by 1975 the rate has quadrupled, and by 1976, $100 million per year was being expended on virus cancer research. We would say that in the last 11 years, the Institute itself has spent $1 billion in this area.

In the years where we had a highlight of this activity, in about a 5-year increment, about 12.5 percent of our total budget has been spent in this particular area.

Now, let me remind you what has been happening, that the area of virus cancer research has allowed the evolution of transforming genes. However, today, we need not talk about oncogenes in terms of viruses anymore. We know that they are separate and they are part of tumor cells. So, if we can look at the rate of spending in this area, we can specifically and precisely identify how much we are spending on oncogenes.

We have very good clear statistics that in 1983, we have spent about $36 million on this specific area, whereas, in the total area of virus cancer research, it is closer to about $90 million, but we can't focus in on this, and we would say that since our Institute has been always very proactive in this area, we are spending about $10 million intramurally and about $26 million goes to the outside, universities, grants and contracts.

So we are thinking, however, that in terms of projection over the next year or 2 years, that rate of research in this area of oncogenes is going to be increasing by about 8.5 percent in 1984 and by a similar amount in 1985. What this means, however, is that this area of research is expanding at approximately twice the rate that the rest of basic research in cancer is expanding, so it is about 4 percent versus about 8.5 percent that the oncogene area has been emphasized by.

In conclusion, I would like to say that the insights from various areas of cancer causation can now be blended into unified cohesive and testable hypotheses at a molecular level. We feel that treatment potential with very highly specific molecular tools will not be far behind, and, as often cited before, the first priority of the National Cancer Institute has always been basic research.

I think the present excitement in this area in oncogene has certainly been a shining example of research success.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Fischinger follows:]

PREPARED STATEMENT OF PETER J. FISCHINGER, M.D., PH.D., ASSOCIATE DIRECTOR, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to present a status report on oncogene research, and to address the direction and opportunities these recent findings may have on the diagnosis, treatment, and prevention of human cancer. You will hear a fascinating story which is a culmination of about ten years of research in the area of virus induced cancer. We used tumor-inducing viruses as a tool to pry open a window on the very secrets of life. These secrets lie in the genes themselves. About two dozen of these genes that we can now identify, isolate, and study, are directly involved in the causation of cancer. These genes have been named as onco (from Greek, meaning tumor) genes. We all have these genes in our genetic warehouse of DNA. Under normal conditions, these genes code for important cellular functions. But we also know how they can go wrong. We have learned much about the switches that make oncogenes malfunction.

NCI has been not only highly supportive of research on viruses and oncogenes, but has also been instrumental in the basic development of these concepts and has shifted resources into this area of research as appropriate. Early concepts of oncogenes and the correct prediction of their being carried about in viruses were first postulated by NCI scientists. The first viral oncogenes were described in early 1976 by three major laboratories--two of which were at the NCI. In 1980, the first oncogenes were cloned in bacteria by two laboratories at NCI. The understanding of the viral switches was greatly enhanced by intramural NCI investigators.

Science in this area is at a very important point. We have experienced a biological revolution and are at the threshhold of a new era in our approaches to cancer. We will discuss the potential for practical applications in the context of modern genetic engineering and advanced concepts of molecular immunology.

NCI's research findings allow, for the first time, the understanding of fundamental processes of how a normal cell becomes a cancer cell. A basic reason for this is that modern biotechnology has allowed unprecedented detailed research into the very structure of molecules of life. One of the most important outcomes has been the fusion of concepts in two different areas of study of cancer causation. We can now say that studies of chemical and biological causation of cancer have ceased to exist as separate disciplines, but are actually united by the concepts of common basic molecular changes at the level of the individual gene.

The National Cancer Institute has already set goals for the year 2000 to reduce cancer mortality by one-half of what it is today, by the application of reasonable preventive measures, and the application of the state of the art treatment. These goals do not include the possible payoffs that could derive from the use of the oncogene research I will discuss today. However, the wealth of this new information makes us very optimistic. We think that it is reasonable to anticipate further reduction in cancer mortality with the applications of findings in the areas of oncogenes.

How the Oncogene Concept Developed

Although this area will be discussed in detail by others, it may be appropriate to define the historical perspective for the recent findings. The earliest insights, starting about twelve years ago, have come from the studies of a class of animal viruses which could rapidly cause leukemias and solid cancers in animals. These viruses were called "retroviruses" because their genetic information existed in the form of RNA, rather than the usual form of DNA. (RNA is a working copy of DNA.) These viruses have the potential to add unwanted genetic information to normal cells. A second important characteristic of retroviruses is that they possess a molecular switching device, capable of turning on various genes. If such a switch or promoter is placed near an inactive gene, it can activate the gene to function in an abnormal way.

Some of the most fascinating retroviruses were those which caused leukemias or solid tumors very rapidly in test animals. These rapid tumor-inducing viruses were unusual because most of them were defective in that they lacked one or more genes needed for their own multiplication. Evidently, after losing their own genes, retroviruses picked up and carried about some specific cellular genes. It was the cellular gene that the virus had picked up rather than one of its own genes that caused the malignancy. This implied that the potential for cancer may be encoded in part in the genes of animals, including man. It is these cellular genes, whose action could result in malignant behavior, that have been named oncogenes. It was clear that a number of rapidly transforming retroviruses could carry about such cellular oncogenes. Up to now about twenty such genes have been isolated. Although the cell has tens of thousands of potentially active genes, it appears that the cell has only several dozen oncogenes.

Another parallel approach which developed within the last five years has been based on the idea that tumor cells themselves could possess turned on oncogenes. Because most human tumors are not known to be associated with viruses, it was thought that if the DNA of the tumor cell itself were transferred to another normal cell, the effect of the tumor cell DNA would be dominant and transform the normal cell to a malignant one. The process of transferring naked DNA from cell to cell, called "transfection", was found to work. Very regularly, scientists could take DNA from most types of tumors and, with a reproducible rate of success, were able to transform apparently normal cells in the laboratory into malignant cells. A particularly important finding was that many of those cellular oncogenes, derived directly from tumors, were essentially the same as several of the oncogenes that were first found to be carried around by the rapidly transforming retroviruses described earlier.

How Does an Oncogene Act?

The next important question was, if the cell has the information for twenty oncogenes, why isn't the cell abnormal? Because all genes act through their protein products, one must examine the status of the oncogene protein itself. Two general alternatives are possible: one, that an oncogene functions excessively; or two, that the oncogene itself has become abnormal in some way, and that the abnormal protein product results in malignancy.

The first possibility of an overproduction of an oncogene product has been clearly documented. We now know that there are retroviruses without oncogenes which can cause tumors but only after a long waiting period. When the DNA of these tumors is examined, the infecting virus or a part of it is found in tumor cell DNA. The critical part of the virus is the powerful "on" switch known as a promoter. This part of the virus has integrated next to a known cellular oncogene, and because of the strength of the promoter, the oncogene became hyperactive. Such indirect activation of cellular oncogenes has been named the "promoter insertion model".

The second form of oncogene activation is a specific mutational change which alters the DNA in an irreversible way. Experiments of this kind with chemical carcinogens have been able to precisely tie in the nature of the chemical action exerted by the carcinogen on the DNA, and the resulting mutational mistake in the DNA of the oncogene. Such an activated oncogene can then be isolated, transfected, and can be shown to act as a transforming oncogene. The fact that most known carcinogens have an effect on DNA, which can cause misreading of the genetic code, implies that the way chemical carcinogens act may be through the specific activation of previously normal cellular oncogenes.

Studies in cancer epidemiology have shown that this disease develops by a multistep process. Therefore, the question arose whether oncogenes also act sequentially, in concert with each other in the laboratory. To test this, normal cells were taken directly from the animal and were transfected with DNA containing a known active oncogene. The cells did not become malignant. However, if a second oncogene was transfected into the same cells, then a full-blown transformation was seen. In other instances, some rapidly transforming retroviruses already carry two different oncogenes. Thus one can identify cancer as a multistep process under laboratory conditions, as well as in epidemiologic studies.

Oncogenes Have a Normal Function in Cells

A very basic question is, what are these oncogenes found in normal cells all about? Are they merely the enemy within, or do they have important natural functions in cell development?

One of the features of any gene is its rate of evolution. A general rule is that genes which are important for basic functions will evolve slowly and remain very similar in all forms of life. When human oncogenes were examined, they were found to be extremely well conserved so that similar genes were found even in fruit flies and yeasts. Because such genes are easier to analyze in lower organisms, it became clear that oncogene-like genes in such organisms act as important growth control signals.

On the human level, we now know that the protein products of several known oncogenes are involved in growth control. The first of these was the product of a monkey-derived oncogene called sis. A computer was used to search for the sequence of the sis oncogene among many other genes which have been sequenced. An almost perfect match was found with the sequence for the normal platelet-derived growth factor (PDGF) gene. PDGF is a small protein found in blood platelets which is very much involved with wound healing and growth repair processes. Another computer search found that the sequence of an avian oncogene, called erbB, was very analogous to a gene coding for the cellular receptor required to bind a small molecule called the epithelial growth factor. Thus, based on these two examples, it seems that cellular oncogenes have a clearly defined, normal function in some cells at some time.

Oncogenes Can Move Around in Cells

Today the specific chromosomes on which most of the known oncogenes are located have been identified. Highly specific chromosomal changes occur in all tumors of certain types, and it was therefore reasonable to suspect that oncogenes may be involved in these changes. In a lymph cell tumor of children, called Burkitt's lymphoma, scientists have known for some time that small pieces of two different chromosomes break off. These pieces are then exchanged reciprocally, so that in the final form the chromosomes end up with wrong pieces reglued to their main parts. These abnormal chromosomes are now known to be directly involved in the cancer process. One of the broken off fragments has a known oncogene, and the major piece of the other chromosome to which this oncogene becomes fused is involved in the control of the synthesis of antibodies. Thus an abnormal situation results in that incorrect reading and expression of an oncogene occurs because of the action of an incorrect control element. A number of other such instances abound or are suspected in other forms of cancer. Sometimes two oncogenes are mutually exchanged between different chromosomes. This area of study is likely to prove useful in developing better diagnostic approaches in cancers whose chromosome changes are more subtle.

One of the observations at the level of chromosomes has been the appearance of abnormal regions within a chromosome which do not stain normally, or by many tiny pieces of chromosomes broken free from the normal structures. This was first seen in certain cancers. We now know that this is due to a vast increase, or an amplification, in the number of genes coding for a particular function. Gene amplification is also a feature of oncogenes. In the course of tumor growth and progression, a number of different cancers have shown an amplification of several oncogenes. Although this is generally a late effect, it can be perceived as making the cell more aggressive and growth independent. Future approaches may well include strategies to interfere with gene amplification.

Possible Opportunities in Diagnosis and Treatment of Cancer

Although at present, most of these findings exist at the research level, modern biotechnology can overcome the technical barriers to bring these advances to the patient's bedside. Recent events in the use of recombinant DNA technology have shown that carrier states of several serious genetic diseases can be identified with certainty at the molecular level by identifying specific changes in the genes. In cancer, the participation and role of built-in genetic changes, which may predispose at least to some cancers, is well known. For example, two childhood tumors have a defined genetic basis. One of these, retinoblastoma, a tumor of the eye, is known to be associated with chromosomal abnormalities, some of which are manifest as a loss of a part of a chromosome. Specific nucleic acid probes could be used to identify the potential carriers of this disease. Similarly, in Wilm's tumor, a childhood tumor of the kidney, a small piece of chromosome II is missing from an area adjacent to the oncogene known to be present on the same chromosome. Again, precise molecular probes not only can detect the specific chromosome abnormalities in the child with a tumor, but may also make it possible to identify the carrier state in the parents of the Wilm's tumor patient.

An expansion of these concepts to other conditions which are known to be strongly predisposing to cancer is underway. For example, there is a hereditary condition known as Gardner's syndrome in which multiple polyps are observed in the colon. It is highly likely that these people will develop colon cancer. Colon cancer cells generally express an activated oncogene. Although the normal cells from unaffected parts of the body of these patients have not displayed activated transforming genes, more studies would be needed in cells of the lining of the colon in which malignant changes first appear. Based on the multistep nature of the cancer process, it may be that other oncogenes, which are not detectable in transfection assays, may already be in an activated state.

The above instances clearly show that specific genetic characteristics render certain populations at increased risk for cancer. However, it is also well known that the most prevalent and potentially lethal carcinogen exposure in man, tobacco smoke, will not affect all individuals in the same way. Many people know very old, heavy smokers who continue to be healthy. On a statistical basis, the heaviest smokers, who are at the highest risk of developing lung cancer, have a 10-20% chance of actually getting the disease. To be able to identify those tobacco users who would be more susceptible to early tumor induction would be of immense benefit. The cancer cells of patients with lung tumors do have an activated oncogene. In contrast, the normal lung cells from the same patient will not have an activated form of the gene, implying that the change occurred as part of the tumor induction, and was presumably initiated as mutational DNA damage by the carcinogen in the tobacco smoke. In all of these cases, the underlying principle is that a genetic change, which could be identified molecularly, would specify a predisposition to malignancy. The knowledge that multiple oncogenes can act in concert, and the availability of known oncogene probes as well as their surrounding control regions, may facilitate identification of the at risk individuals.

Attack on the Oncogene Product

One of the exciting areas has been the identification of the protein products of the activated oncogenes. Because activation is associated with a change in the DNA, the resulting protein will also have different structure as well as properties. The new and powerful monoclonal antibody technology can identify changes on the surface of a protein with great precision. Thus one can develop antibodies to a site on the activated oncogene protein which can differentiate between the product of the activated oncogene and the normal non-activated cellular oncogene.

Monoclonal antibodies can also be armed with radioactive tracer molecules, to zero in on small areas of tumor cells undetectable by any other diagnostic method. Alternatively, monoclonal antibodies could serve as carriers for drugs and toxins to deliver treatment directly to the tumor cell. The specific recognition of a cell, which has an abnormal oncogene protein, by such an armed antibody would be valuable in both pathologic diagnosis and treatment. We already have monoclonal antibodies to tumor-specific surface proteins of many cancers. These antibodies are already being used experimentally for the diagnosis of distant tumor spread. A potential limitation of this approach is that not all tumor cells will make enough protein antigen for identification. Furthermore, tumor cells can turn off proteins if these are not needed for the maintenance of the malignant state.

A possible strategy may be to attack the protein product of the activated oncogene itself by monoclonal antibodies. This should work because the oncogene protein is the key which makes the cell malignant. One of the problems, however, is that only some of the oncogene products are present at the cell surface. The activated proteins of other oncogenes lie underneath the cell membrane or even in the nucleus of the cell. New technologies are now being explored at the National Cancer Institute to bring armed antibodies or their fragments to the inside of the cancer cell.

Another problem that has been observed is that oncogene amplification is proportional to the degree of malignant behavior. For example, a promyelocytic leukemia cell line, which consists of immature white blood cells, will have a greatly increased number of copies of an oncogene, which are overproducing the protein product. However, there are drugs which under some circumstances seem to be able to reverse the amplification process; with treatment, the cell loses the extra copies of the oncogene and becomes more like a mature normal white blood cell. This area of cancer research, which deals with a redirection of a cancer cell back to normalcy, is gaining considerable impetus.

History of Funding

The success of oncogene research can be directly traced to support of virus cancer research which began to expand significantly in 1970. In that year, $ 21 million was spent. In 1975 the total had quadrupled. By 1976, the total amount of combined extramural and intramural research for all funding mechanisms rose above $ 100 million per year, and it remained at that level until 1981. During the next two years, under continuing resolutions, the National Cancer Institute's total budget remained essentially level. Whereas prior to 1981 all oncogene research was associated with virus cancer research, after this time a significant amount was beginning to be spent on cellular transforming genes which were technically not associated with viral research. During the top five years of virus associated cancer research, 12.5% of the entire NCI's budget was expended in this area. During the last two years, the proportionate amount of NCI's total budget spent on virus cancer research was about 9%, or $ 90 million. It is noteworthy that the total amount spent on cancer virus research in the last eleven years just exceeded one billion dollars.

Within the past few years, research on oncogenes has become clearly identified in its own right so that funding allocations could be more precisely defined. In 1983, the total amount expended on pure oncogene research was $ 36 million, which represented 3.7% of the total NCI budget. The specific breakdown into NCI intramural research and extramural support shows that $ 10 million and $ 26 million of the total were spent on oncogene research by each sector respectively. The proportion of cancer research defined as strictly oncogene research is rising, and is expected to continue to go up by 8.4% in 1984. Our research budget projections indicate a similar growth into 1985.

Summary

Insights from various areas of carcinogenesis can now be blended into cohesive and testable hypotheses at a molecular level. One can now define new areas such as biochemical epidemiology. Whereas previously one thought of identifying individuals at high risk for cancer due to lifestyle or occupation, one can now propose to identify the susceptible individual at the molecular level for some cancers. Theoretically, if past exposure to carcinogens were significant, we may now be able to measure the exact sites of attack and damage in cellular DNA. We now have oncogenes as the probable targets. Treatment potential with highly specific molecular tools should not be far behind. As often cited before, the first priority of the National Cancer Institute has always been basic research. The present excitement in the area of oncogenes has certainly been a shining example of research success.

Mr. **Gore**. Thank you. We are going to have some questions, but we will wait until the panel has been completed and Dr. William Feller is president-elect of the American Cancer Society. Dr. Feller, we're delighted to have you here. Without objection, your statement will be included in the record and if you could summarize your prepared remarks, we'd appreciate it. We're delighted to have you here. Please proceed.

Dr. **Feller**. Mr. Chairman, and members of the subcommittee——

Mr. **Gore**. Why don't you——

Dr. **Feller**. This microphone here?

Mr. **Gore**. No, that one there. Yeah, there you go.

Dr. **Feller**. Mr. Chairman, and members of the subcommittee, I speak as a private citizen and a member of the scientific cancer research community. My present professional activities at Georgetown University School of Medicine include the teaching of medical students, cancer research activities and the care of cancer patients.

I might add, I've been active in the field of cancer research for the past 25 years. I've also been a professional volunteer of the American Cancer Society for 15 years and currently am the president-elect of the District of Columbia Division of the American Cancer Society. I speak on behalf of the American Cancer Society today.

I want to just state that the American Cancer Society is one of the oldest private cancer research organizations in the United States. It was founded in 1913. We do not receive Federal funding. This current year, we will spend over $62 million for cancer research activities.

My remarks will be confined to the overall significance of oncogene research in a historical perspective. I shall also try to give my views on the possible future direction.

I think that one can summarize the discoveries by saying that the discoveries of oncogenes and their action in the cancer cell has been the single most important development in modern cancer research studies. I think many experts really feel that it is the most significant advance in the last 50 years.

The knowledge that specific cancer-causing genes occur in human and animal cancer cells represents a dramatic conceptual breakthrough. I want to stress, as you have mentioned, Congressman Gore, that while this is a dramatic conceptual breakthrough, that the treatment strategies that we are hoping to see will be at least perhaps 10 years away. There may be some differences of opinion there. I would liken the discovery of oncogenes to the discovery of the tubercle bacillus by Robert Koch in 1880. Now, certainly, this was a major conceptual breakthrough that infectious diseases were due to specific biological units and this did lay the foundation of modern bacteriology. But if one reflects, it was almost 60 years before treatment strategies based on the discovery of the tubercle bacillus were available.

Now, I am not suggesting that we're going to have to wait 60 years, but I think that certainly, as you have said, this is a conceptual breakthrough. Scientists can now direct specific questions much more accurately, but I would really say that the treatment strategies would be, I think, at least 10 years away. Now, again, that is a guess.

Well, again, Dr. Fischinger has gone over the history of this and I want to again mention that I suppose, everybody says, that these concepts grew out of what we would call RNA tumor virology and that discovery goes back to 1911 when Dr. Peyton Rous, of the Rockefeller Institute, discovered a filtrable agent which caused chicken sarcoma and I suppose that would be the birth of what we would call RNA tumor virology.

Over the 70 years since then, of course, this field of RNA tumor viruses has developed slowly at first, but very rapidly in the last 10 to 15 years, and in 1970, Dr. Duesburg and Dr. Peter Vogt showed that the Rous virus contained a cancer gene and I think that, again, was a major landmark, and finally, in 1976, of course, this cancer gene occurring in the virus was isolated.

Now, the whole field of RNA tumor virology went ahead. There were many other animal cancers that were caused by RNA tumor viruses, and finally in 1981, Robert Gallo, of the National Cancer Institute, has isolated a human RNA tumor virus from several patients which most scientists believe is associated with a human leukemia.

By 1976, scientists had shown that the cancer virus was in the RNA tumor virus, the Rous sarcoma virus. This could be found in virus-free animals. By the middle of the 1970's, we began to think that these cancer genes associated with viruses were found in normal, uninfected cells. So again, I think the concept took off at that time.

Well, I won't go into the background. I think you have a number of distinguished scientists here today who will give you the present knowledge of the mechanisms of oncogenes. I just want to say a few words about the future of research directions.

As I mentioned before and I think it's very important, as you mentioned, Congressman Gore, not to give the impression that this oncogene breakthrough is going to result in new treatment strategies immediately. It is possible, certainly, within 10 years.

I think that the questions that you raised regarding the possible speed of the clinical application and the role of accelerated funding—I think that is a very important question and I might add that the American Cancer Society is currently arranging a meeting of cancer scientists to explore this question of accelerated funding.

As Dr. Fischinger has mentioned, certainly I think there are many ideas of how to proceed. We do have highly sensitive agents for detecting the presence of oncogenes and oncogene products. These are being developed very rapidly. Just a few weeks ago, Dr. Marty Cline, of Los Angeles, published in the Science Magazine a first attempt that I recall to classify human cancers according to their oncogene characteristics. So I think we will see very rapidly that we can classify cancers according to their oncogene characteristics or expressions.

I would say that our present-day monoclonal antibody techniques are extremely sensitive. We at Georgetown have been utilizing them for a possible development of a blood test for the detection of early breast cancer. Our preliminary work shows that we can detect some of these antigens in patients' blood in well over 95 percent of early breast cancer. We, of course, do not know that these are related to oncogene products, but the technology is there.

Dr. Fischinger also testified on the fact that we can detect oncogene expression in patients with benign tumors and thereby get a signal that a particular individual is at a high cancer risk.

In the question of cancer treatment, as Dr. Fischinger indicated, we are, of course, moving ahead. The very fundamental question, of course, is the concept of switching the cancer genes off, and I think that Dr. Howard Temin perhaps later today will tell us what is the possibility from our basic knowledge today of whether this is a realistic goal.

The other strategy that we are thinking in terms of, the scientific community, is the concept of blocking the oncogene protein product. As Dr. Fischinger mentioned, the oncogene acts through an oncogene protein—that is, when the oncogene is expressed, it—causes the translation or the formation of a specific protein product and it is that protein product which actually causes the cell to take on a malignant characteristic and I think that the strategies that we are thinking of at this time include those strategies of neutralizing or blocking that cancer-causing protein. And I think that those strategies are being certainly developed or thought about.

Now, finally, let me just address this question of accelerated funding. I know that this subcommittee and the Congress might well ask that question of whether increased or accelerated funding in this area might speed up the delivery of useful clinical strategies.

Certainly, as Dr. Fischinger mentioned, there have been precedents for accelerated funding, and of course, the most notable, perhaps, in the Cancer Institute has been the Special Cancer Virus Program which was instituted in 1970. I think this represents a successful accelerated funding program.

I might say aside, Congressman, that at the time that this special funding and this accelerated program was set, it was thought that perhaps human cancer was caused by a virus, an RNA tumor virus, and while that hasn't been fully realized at this time, I think we should stress that the basic research that flowed from these studies set the stage for the oncogene knowledge of today.

So, again, as Dr. Fischinger said, the NCI really has stood for basic research and the RNA tumor virus program was developed along those lines and that research, although it hasn't caused—we haven't seen a—that viruses in general, or certainly RNA tumor viruses are major causes of human cancer. The knowledge that we are dealing with today, I think, largely grew out of that program and that money.

Well, I would recommend or I would suggest that the Congress certainly consider perhaps accelerated funding in a somewhat broader targeted category and that is really the regulation of gene expression. I think that if one looks at oncogene research today, it is largely one facet of the overall field of gene regulation and certainly Dr. Temin will speak to that.

I suppose that one can say that oncogene research really is on the cutting edge of this field of gene regulation, but I think that perhaps the committee might wish to look at that entire field. I think that increased funding in the area of oncogene or of genetic regulation would be of immense benefit to the United States. Again, as I have stressed, that while it is very promising in the conceptual thing, the treatment strategy to be delayed.

Let me just summarize by saying that perhaps it might be appropriate if the Congress were to ask the National Cancer Institute and the American Cancer Society, perhaps the National Academy of Sciences, to perhaps develop a position on this question. I think that you have three very distinguished scientific bodies here who could report back to the Congress, perhaps in 6 months or 1 year, on this question of, one, would accelerated funding be appropriate; and two, if it is, what would be the strategies?

I would like to end by saying that I think that if the United States is to maintain its position as the technological leader of the free world, certainly I think increased money to speed the benefits of the genetic revolution are warranted.

I thank you, ladies and gentlemen, for the opportunity to present my views on oncogene research.

[The prepared statement of Dr. Feller follows:]

PREPARED STATEMENT OF WILLIAM F. FELLER, M.D., PH.D., ASSOCIATE PROFESSOR OF SURGERY, GEORGETOWN UNIVERSITY AND PRESIDENT-ELECT, DISTRICT OF COLUMBIA DIVISION. AMERICAN CANCER SOCIETY

Mr. Chairman and Members of the Subcommittee:

I appear before your Subcommittee today to speak to the subject of oncogene research and its implication on the control of cancer. I speak as a private citizen and a member of the scientific cancer research community. My present professional activities at Georgetown University, School of Medicine include teaching of medical students, cancer research activities, and the care of cancer patients. I have also been a professional Volunteer of the American Cancer Society for fifteen years and currently am the President-Elect of the District of Columbia Division of the American Cancer Society. I am privileged to testify today on behalf of the American Cancer Society. My remarks will be confined to the overall significance of oncogene research in a historical perspective and how this type of research relates to the overall cancer research effort. I shall also try to give my views on possible future directions.

Overall Significance of Oncogene Research

The discovery of oncogenes and their action in the cancer cell has been the single most imortant development in modern cancer research studies. The knowledge that specific cancer causing genes occur in human and animal cancer cells represents a dramatic conceptual breakthrough which will change the course of current cancer research. Scientists now have a new and precise way of looking at the causative mechanisms of cancer at the cellular level. The oncogene or cancer gene concept grew out of the vast body of scientific knowledge which accumulated with the studies of RNA tumor viruses over the past 70 years. The discovery of oncogenes is analogous to the discovery of the tubercle bacillus by Koch in 1880. The identification of the causative agent of tuberculosis laid the foundation of modern bacteriology and led to techniques for early diagnosis and ultimately antibiotic treatment of tuberculosis.

Today, scientists have discovered the biological unit - the oncogene - whose improper activity causes cancer in animals and in man. There are about twenty of these oncogenes that play a role in the causation of cancer.

We are now beginning to dissect the molecular events leading to the malignant transformation of a normal cell. The major molecules acting in the cancer process and the outline of how these molecules interact one with another in the malignant process are already in view and the exact details of these biochemical processes are rapidly being elucidated.

Development of the Oncogene Concept

The story of oncogenes really goes back to 1911 when Dr. Peyton Rous(1) identified a virus - then called a cell free filtrate - from a chicken sarcoma. He showed that he could transmit or initiate a new cancer in chickens with this cell free preparation. Thus, RNA tumor virology was born. In the 70 years since then, the Rous sarcoma virus has become the most widely studied animal cancer virus. Eventually, the cell free preparation was shown to contain an RNA tumor virus. In 1970 Duesberg and Vogt(2) showed that the Rous virus contained a cancer gene or oncogene. Subsequent work clearly showed that the oncogene in the Rous sarcoma virus caused cancer to develop in susceptible cells. Defective Rous sarcoma viruses without the cancer gene did not cause cancer. The cancer gene was isolated in 1976 by Stehelin,.et.al(3)(Bishop's laboratory).

Other types of RNA tumor viruses were discovered during the intervening years. In 1936 Bittner(4) isolated a "factor" in mouse milk that caused breast cancer in mice. Ludwig Gross(5) in 1951 demonstrated that mouse leukemia could be transmitted by a cell free filtrate. By the mid 1960's RNA tumor viruses had been isolated from a wide variety of animal tumors. Such diverse tumors as mouse breast cancer, mouse leukemia and sarcoma, bovine leukemia, cat leukemia and cat sarcoma - all of these cancers were shown to be casually related to RNA tumor viruses. Although extensive attempts to isolate a human RNA cancer virus had been made by 1970, no human RNA tumor virus had been isolated at that time. Finally in 1981, Robert Gallo(6) of the National Cancer Institute isolated a human RNA tumor virus from several patients with a certain type of leukemia (human T-cell leukemia).

The discovery and identification of the Rous sarcoma virus oncogene was a pivotal event in oncogene research. It clearly established that the presence and activity of a single gene in an animal cell could cause cancer. The identification and isolation of the "transforming cancer protein" by Brugge and Erickson(7) in 1977 further strengthened the oncogene concept.

Many activated genes initiate a process and provide the necessary information for the ultimate development of a specific protein. These gene encoded proteins are generally enzymes or structural proteins which are necessary for the normal maintenance of cellular processes. The "transforming cancer protein" of the Rous sarcoma virus was found to be changing some fundamental property of the normal cell so it became a malignant cell. The detailed molecular events of the malignant transformation of a cancer cell could now be studied with this model. By 1980 the outline of the present oncogene theory was clearly in place. It was known that many, though not all, of the animal RNA tumor viruses could transform certain types of normal cells into cancer cells in the test tube. Like the observation of Duesberg and Vogt with the Rous sarcoma virus, it was observed that all of the "test tube transforming" RNA tumor viruses carried a single gene that causes cancer. These viral type oncogenes were the responsible agents for the malignant transformation seen in the test tube.

The molecular biology of the RNA tumor viruses and how they act inside of infected cells was also well known by 1980. RNA tumor viruses belong to a class of viruses called retroviruses. The genetic information of these types of viruses is carried in the form of RNA and additionally they carry an important enzyme, reverse transcriptase, in the virus packet. During their life cycle inside of a cell, the RNA genes are copied into DNA, and this new DNA segment or gene is integrated into the cell's genes. If the RNA tumor virus carries an oncogene, that gene is incorporated into the cell's genetic apparatus and will generally be activated and expressed. The expression of this newly acquired oncogene by the cell causes the cell to become malignant. As long as the cancer gene is active, the cell is malignant. If the gene is switched off the cell loses its malignant character and becomes a normal cell. But the critical question was, where did the oncogene itself come from? Was it always a viral derived gene or could it have originated in animal cells? The final answer - now clearly established - has shown that the viral oncogene was really a copy of a cellular gene - a proto-oncogene. Thus, today we know that cancer genes are normal components of all animal cells.

Cellular Oncogenes

How did we get scientifically from viral oncogenes to cellular oncogenes? In 1969, Huebner and Todaro(8) had noted that leukemia in mice could be transmitted through the germ cells and because of this observation they postulated the existence of a "cellular oncogene". They postulated that most if not all animal cells had cellular oncogenes which could under the appropriate circumstances cause cancer. It was the work of Stehelin, Varmus, Bishop and Vogt(9), in 1976 that clearly showed that cells of virus free birds (chicken and quail) contain cellular oncogenes identical to the viral type oncogenes seen in the Rous sarcoma virus. These findings of cellular cancer genes highly related to viral type cancer genes were soon extended to cells of other animals - cells of all vertebrate species. Thus these critically important studies established the central thesis of the oncogene theory: Oncogenes are normal components of all animal cells. How these cancer genes act to cause cancer has been broadly worked out the past six years. Today there is a general outline of an oncogene mechanism. Several details are missing and the precise mechanisms of control are unknown but, the protein products encoded by several cancer genes are known and their function in some malignant cells has been defined.

Cellular Oncogenes Demonstrated by Direct Gene Transfer

Recently (1979) human cancer genes have been isolated using more direct gene transfer methods. Three American laboratories have accomplished these direct cancer gene isolations. (Weinberg, MIT; Cooper, Harvard Medical; Wigler, Cold Springs Harbor). Using the methods of gene cloning, Weinberg and his colleagues(10) extracted single genes from human cancer and transferred these single cancer gene units to normal animal and human cells. These transferred cancer genes caused the normal cells to become malignant. It was quickly noted that many of these oncogenes isolated from nonviral type animal cancers or from human cancers were almost identical to the viral type oncogenes of the RNA tumor viruses. Thus, using data obtained from two diverse technologies, i.e. viral oncogene probes and direct gene transfer, it has been established that human cells contain several cancer causing genes. These genes are either mutated or have become switched on inappropriately in human cancer cells.

Present Concepts and Postulates of the Oncogenes Theory

1. There are about 20 known human cancer genes. Probably 10 or 20 more exist but have not been identified.
2. 19 viral type oncogenes have been identified. Cellular cancer genes related to most of these have been found in normal cells of man.
3. Cancer genes play an important role in many if not all normal cells at some point in their development. Their activity in normal cells seems largely related to the growth signal systems of normal cells. Many normal cells are known to express or exhibit oncogene activity as part of normal growth and differentiation processes.
4. Cancer genes follow classical Mendelian Laws in general.
5. Most cancers probably express abnormal activity of at least two oncogenes. A recent study of oncogenes expressions in "fresh" human tumors revealed the expression of four oncogenes in most cancers studied. Some cancers exhibited expression of seven different oncogenes.
6. Oncogene expression has been detected in some "fresh" human cancers as well as in human cancer cell lines.
7. The protein products of several (5 or 6) oncogenes have been identified and isolated. Two types of function have been assigned to oncogene proteins: Several oncogenes encode a protein that is a tyrosine specific kinase. This

enzyme may function to regulate growth factor receptor status. Some cancer genes encode or produce a protein that binds to DNA and could thus act to regulate or control other genes. Two oncogene protein products are growth factor receptors (or parts of a growth factor complex).

8. Two mechanisms probably account for the conversion of normal acting proto-oncogenes into cancer causing genes:

   (1) A carcinogen stimulates the cancer gene into greater activity and thus allows the gene to produce a much higher level of protein product than normal. (100 fold increase in oncogene product has been reported in some cancers).

   (2) A carcinogen "mutates" or damages the "normal oncogene" and thus a structurally abnormal protein product is formed which loses its normal cellular function. Both mechanisms probably occur. Most cancer genes probably operate by inducing higher levels of protein product. (C-ras ^{Ha}), a type of oncogene, is known to contain a single point mutation (damaged or changed DNA sequence). How prevalent this gene or other "mutated" type cancer genes are in human cancer is unknown.

Future Research on Oncogenes

It is likely that the breakthrough on oncogenes will open several new strategies for cancer diagnosis and treatment within the next decade. Whether accelerated funding for research in the field of gene regulation would speed possible clinical applications of oncogene knowledge is an extremely important question. The American Cancer Society is currently arranging a meeting of cancer scientists to explore this question.

1. Cancer diagnosis: Highly sensitive reagents for detecting the presence of oncogenes and oncogene protein products are close at hand. The first attempt to classify human cancer according to their oncogene characteristics has been recently published (Science, April 20, 1984)(11). If cancer patients shed oncogene protein products in their blood these could be used to detect cancer at a very early stage. Present day monoclonal antibody detection techniques are extremely sensitive. Preliminary work in our cancer research laboratory at Georgeotwn University using two monoclonal antibodies developed in the Netherlands Cancer Institute in Amsterdam, has resulted in a possible blood test for early breast cancer detection. This test is 95% accurate in our hands. Extended clinical studies are now in progress. The Dutch monoclonal antibody detects differentiation antigens shed by cancer cells in the blood.

The possible relationship of these antigens to oncogenes is unknown.

If oncogene protein products are released in the cancer patient's blood, perhaps, they can be detected by similar immunological techniques. If cancer gene products are not released, small needle biopsies of normal tissues can be analyzed for oncogene expression. High degrees of oncogene expression could signal a high cancer risk status. Regular cancer surveillance tests or even prophylactic drugs could be used to prevent the development of full blown invasive cancers in these types of patients. In the area of cancer prevention the fundamental question is what agent or agents turn the cancer gene on in the first place? Precise answers to this question would have far reaching consequences in the field of cancer prevention.

2. Cancer treatment. Can the Oncogene derived knowledge of the molecular events occurring at the cellular level in carcinogenesis lead to new treatment strategies? The most fundamental question in this regard is: Can we devise strategies to switch off cancer genes? From animal studies we know that if we switch off or repress the activity of an oncogene, that cell is no longer malignant. The switched off cell behaves as a normal cell. The mechanisms for turning off gene activity are poorly understood at present. If the switch off strategy eludes us, then strategies to neutralize

or block the action of oncogene products seem feasible. Since the activated oncogene acts on the cell through a protein product intermediary, interference with this "cancer causing protein" could be deleterious to the cancer cell. Several new treatment strategies will undoubtedly be developed over the next ten years based on the molecular knowledge resulting from oncogenes studies.

Possibility of Accelerated Funding for Oncogene Research

This Subcommittee and the Congress might well ask whether increased or accelerated funding in this area of cancer research might speed up the delivery of useful clinical strategies based on oncogene derived knowledge. A precedent for accelerated funding of targeted types of cancer research was set by the Congress in the late 1960's. Indeed, the Special Cancer Virus Program of the National Cancer Institute is a prime example of a successful "accelerated funding program". Between 1970 and 1976 the amount of monies spent on virus cancer research quadrupled ($21 million to $85 million). By 1976 over 100 million dollars was spent in the United States annually on virus cancer research. I believe that Dr. Fischinger's testimony today will indicate that the amount of money spent on "pure oncogene research" in 1983 was 36 million dollars, about 3.7% of the total National Cancer Institute's budget.

If the Congress were to consider accelerated funding in this field, I would recommend a somewhat broader targeted category - that of the regulation of gene expression. Oncogene research today is largely one facet of gene regulation. Advances in the general knowledge of gene regulation would likely be very helpful to oncogene research. Conversely, oncogene research appears to be on the "cutting edge" of the field of gene regulation. Perhaps, the Subcommittee can develop data on the resources presently allotted to the overall field of gene regulation. Increased funding in this area of biological research would not only speed up oncogene research but yield broad benefits to society in many fields. The practical fall out of this type of basic research - gene regulation - to other areas of human disease and also to agriculture genetics and agricultural productivity could be immense. If the United States is to maintain its position as the technological leader of the free world certainly increased money to speed the benefits of the genetic revolution seem warranted.

Thank you ladies and gentlemen for the opportunity to present my views on oncogene research and its implications on the problems of cancer control.

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Mr. GORE. Thank you very much.

Let me ask some broad overview questions, if I can, and then we'll get into some of the finer details with later witnesses.

Dr. Fischinger, if your optimism turns out to be justified, by the year 2000, what would you expect the survival rate to be for cancer? What can we hope for as a result of this family of breakthroughs in oncogene research?

Dr. FISCHINGER. It is always a bit hazardous to guess in terms of numbers. I would say that maybe even as of today, our survival in terms of major cancers is approximately 50 percent. We recognize that our statistics are always working backward by several years as we do the analysis and as we say that, if by year 2000, we can reduce that mortality in half, we would be talking about the 75-percent survival of all the people that actually come down with cancer. This is a 5-year survival, Mr. Chairman, and we, however, know that for the great majority of cancers, if you survive for 5 years—of course, there are exceptions—then you have a very good possibility of surviving for the next 15 years, which de facto, means that you're probably cured.

Mr. GORE. Which means you're going to be killed by something else. [Laughter.]

All right. Now, the 75-percent figure, is that a figure that we ought to be using? Are you saying that if your optimism is justified, then, by the year 2000, we ought to be able to expect a 75-percent survival rate for cancer?

Dr. FISCHINGER. Let me say, this is a theoretical possibility because there are a number of things that have to be considered on a larger scale. With those figures that we cite are cancers, such as lung cancer, that can be reduced by an enormous amount if people stop smoking. I think the idea of educational campaigns to see how effective this will be, especially in our younger population that is starting to smoke now.

Mr. GORE. Uh-huh.

Dr. FISCHINGER. If this is effective, then we can do this, but I would say there are many caveats relative to these projections.

Mr. GORE. I'm principal sponsor of legislation to toughen the warning labels on cigarettes and advertising and also to begin an aggressive educational program on that subject, but I want to stick here with oncogene research and look a little more closely at some of these survival rates.

The survival rate for some cancers, pancreatic cancer, for example, has risen from 1 percent to 3 percent, and although this can be looked on as a threefold increase, it is so tragically low that that increase really doesn't have that much significance. It does to some people, but overall, it doesn't have that much significance.

Now, do you think that the oncogene research, which we are looking at in this hearing today, do you think that oncogene research will have an impact on these kinds of cancers where we currently have an extremely low survival rate?

Dr. FISCHINGER. Again, this is very much a projection. I think you certainly have picked on one of the least successful types of cancer in terms of treatment and prevention. One of the reasons, of course, is that the pancreas is very hard to get to. The symptoms usually come up late and the tumor has essentially spread.

I think a very early diagnosis in pancreatic cancer would be very useful. Whether this is due to technology such as nuclear magnetic resonance or some of those technologies, or whether we could in some way define some molecule that would be in the circulation, for example, in the blood, that would indicate to us that early pancreatic cancer is actually starting. If we have that, then we can intervene early enough——

Mr. **Gore**. Yeah.

Dr. **Fischinger** [continuing]. And we hopefully think that perhaps there may be cancers that will have some products of activated oncogenes that may be involved.

Mr. **Gore**. Uh-huh.

Dr. **Fischinger**. I would say probably some other forms of intervention and treatment will come before the oncogenes themselves, so that survival from pancreatic cancer specifically can be elevated.

Mr. **Gore**. Perhaps transplants, which are coming onstream—another subject this subcommittee has looked at. Well, oncogene research has implications, not only for treatment, but also for early detection and also, as we hear in more detail from later witnesses, implications for screening to target preventive strategies, environmental and diet, and others, lifestyle.

So presumably with the combination of those three approaches, the very low survival rates for cancers like pancreatic cancer can also be raised fairly significantly. It is not too much to hope for, is it?

Dr. **Fischinger**. No.

Mr. **Gore**. Dr. Feller, did you want to respond to the questions that I have asked of Dr. Fischinger. First of all, what would you expect to be the survival rates in the year 2000? If you could swing that microphone around there, yeah.

Dr. **Feller**. Well, I think that perhaps I'm a little more optimistic than Dr. Fischinger here. He speaks, of course, for a very august governmental agency and perhaps, therefore, is more conservative, but I would say that I would believe by the year 2000 that we will see cure rates, five-year survivals, in the 90-percent figure.

I think that that is a big optimistic jump, but I think, Peter, you did distinguish in your testimony between current knowledge—you have already predicted a 75-percent survival for the year 2000, Dr. Devita has already testified to that—without taking into consideration the oncogene knowledge. And if I may, Congressman Gore, I think that going to the pancreas, I think that it is obvious to most scientists today that we really are going to have to rely on blood tests for early detection.

Mr. **Gore**. Yes.

Dr. **Feller**. We do have these other strategies, the NMR, but I think in terms of cost, which certainly the Congress is mindful of, that we are going to have to develop screening techniques that are within the cost of the present health care budget. And I think that we are already seeing, even before we have the oncogene products in our hands, we're beginning to see monoclonal antibody techniques.

I might say that I was at the cancer meetings in Toronto this spring and I think that there were scientists who were showing us antigens that were picking up 60-, 70 percent of pancreatic cancer by a blood test, so I think that the oncogene research stimulus will lead us, within perhaps 5 to 10 years, to relatively accurate blood test screening.

What was your other question?

Mr. Gore. Well, first of all, let me focus back in on that. As president-elect of the American Cancer Society, you're telling us this morning that these new breakthroughs in oncogene research now make it likely that by the year 2000, just 16 years from now——

Dr. Feller. Right.

Mr. Gore [continuing]. We may very well see a 90-percent survival rate for cancer?

Dr. Feller. These predictions, obviously, are very difficult when one is dealing in the realm of scientific research or knowledge. It is very difficult, but I would say, yes, in my experience, I think in 16 years, given the present impetus and the present level of funding, I would think that is possible—I use the word "possible."

Mr. Gore. Well, now, just to restate it, within 16 years, you believe that the survival rate for cancer in the United States——

Dr. Feller. For most cancers, right.

Mr. Gore [continuing]. For most cancers in the United States could well be as high as 90 percent. Is that correct?

Dr. Feller. That is correct. That is correct.

Mr. Gore. All right. Now, let me recognize my colleague and I'll come back and ask the other questions because I have taken too much time. Let me recognize Mr. Skeen.

Mr. Skeen. Thank you, Mr. Chairman, and I think your time was well spent. I think this is a great combination we have of the risk-taker on the one side here, and the one that wants to step out and say the other one is characterized by his colleague as a little more conservative. I think that's a good approach to this particular question.

What is the 5-year survival rate now, percentagewise, for all types of cancers?

Dr. Fischinger. Fifty.

Mr. Skeen. About 50 percent?

Dr. Feller. About 50 percent.

Dr. Fischinger. Fifty percent.

Mr. Skeen. About 50 percent. I think that's an amazing record in itself, given the progress since say, the 1950's, for instance, which is within the grasp of some of us here, but maybe not all these young fellows sitting around here.

I would like to ask this question of both of you. I'm a little concerned. The basic research and the conceptualization that goes into the oncogene research and some of the rest represent small steps forward. To you, they are very large steps, I'm sure. To the general public, the work on cancer has always involved very small steps forward, which I think accumulate into something that has given us these kinds of percentages. What I am concerned about is the funding that you've talked about this morning for the kind of research, $1 billion over 11 years doesn't seem like an awful lot of money for something as serious as this kind of a problem, and one which I think most of the people in the United States are so dedicated to.

With the changes that you've had in concept, how closely do diagnostic techniques follow and who does that kind of work? Is it those who are the researchers or those who are closely associated with the researchers that come up with the original concepts? How closely followed is the diagnostic technique, because I notice that in many types of cancer, the diagnostic techniques have changed rapidly in the last 10 years, for instance, and they've become easier and easier, for instance. And then how do we—and I'd like to have you comment—how do we educate the general public to take the stance that, "Well, I'd whole lot rather go through these diagnostic procedures if they're easy enough and if they can be self-applied," or whatever, like the blood tests and some of the others, and I'd appreciate a comment. Just how closely related is the diagnostic technique with the concept, because things change so rapidly, I'm afraid sometimes we're so far ahead in concept that we're way behind in technique.

Dr. **Fischinger**. Let me address this point by saying that categorically, it is very difficult to give an overall figure. Depends very much on a specific task and the application of it and the need and the acuity.

Let me give you, just as an interesting aside as to what has come out of virus cancer research and how rapidly such a test could be applied. For example, one of our researchers, Dr. Robert Gallo, who has been working on a virus that causes adult leukemia in people, so-called adult T-cell leukemia. He has found a virus causes this and he has been working on this virus and, as an aside, almost, he also looked at the fact whether, in this highly publicized disease AIDS, such viruses may be involved and you have probably all read very recently that a very similar virus called HTLV3 is involved in AIDS. The idea is, because this is such an acute problem, that we can translate the technology of having a blood test for AIDS—in other words, where we can examine literally tens of millions of transfusion samples in the United States—well, this test will probably go into effect from the research level, and at a time of transfer to industry, we're only expecting about 6 months or so. This, I think, is probably really, the salient example of how rapidly this can be done, because we are quite certain that this is what's happening.

Mr. **Skeen**. So you've pretty well got a straight transition——

Dr. **Fischinger**. Yes.

Mr. **Skeen** [continuing]. Into this system and a rapid response.

Dr. **Fischinger**. And some of the other kinds of tests, of course, you have to do a lot of studies. You have to do controlled clinical trials to see how effective they are. The process of developing, and permission from the FDA to do this will also take some time. I would say in most cases, the time process is more consuming, but specifically, it's the relationship of how strong the scientific base is between a test and a real observation that you have a tumor ongoing.

So I would say the shortest interval of time is something. It could be about 6 months. It may take years, however.

In terms of the question of educating the public, I think this is a very important critical step. Obviously, I think Dr. Feller can certainly address himself to this because of his expertise in breast tumors, how effective some of these various modalities can be and I think he's probably even much closer to the patient herself in this case.

Mr. **Skeen**. All right.

Dr. **Feller**. Well, Congressman Skeen, and Congressman Gore, let me just reflect. Going back to that 90-percent figure, Congressman, I want to point out that today, we are curing about 70 percent of women that appear in our office with breast cancer. That is, about 70 percent are being cured.

Mr. **Gore**. But overall, it's still 50.

Dr. **Feller**. Overall, but you have to break down the cancers into types. Now, you focused on pancreatic, but may I point out that breast cancer is the most common cancer in women. It occurs in about 25 percent of all cancers in women, and this type of cancer is about 70 percent curable today.

And if we were to apply the mammographic techniques which we have today, we could increase that survival to 80 percent.

Mr. **Gore**. Would you yield——

Mr. **Skeen**. Surely.

Mr. **Gore** [continuing]. For me to follow up on this?

Mr. **Skeen**. I think it's a good point.

Mr. **Gore**. Now, specifically on breast cancer——

Dr. **Feller**. Fine.

Mr. **Gore** [continuing]. Oncogene research has resulted in a brand new detection technique——

Dr. **Feller**. Well, I would——

Mr. **Gore** [continuing]. In the Netherlands and I'm wondering first of all, will this be the first product of oncogene research used on human patients and what would you expect results of breast cancer detection to be with the use of this new Dutch technique?

Dr. **Feller**. Let me go into that, Congressman. That represents the work in our laboratory at Georgetown. We have been collaborating with the Netherlands Cancer Institute——

Mr. **Gore**. So that's the Dutch/Georgetown technique. [Laughter.]

Dr. **Feller**. Right, it's the Dutch/Georgetown. I know the Dutch are very much in the news these days, but I do, Congressman, want to be sure——

Mr. **Gore**. We've had a tendency to downplay——

Dr. **Feller**. I know.

Mr. **Gore** [continuing]. America's role in some of these new prizewinning developments, so let's not do that here.

Dr. **Feller**. I'd like to state that we have collaborated with the Netherlands Cancer Institute. I might say just technically, at Georgetown, we have developed the actual technological technique. They had provided us with these monoclonal antibodies, but they were unable to apply them to a blood test and during the past year, we, at Georgetown, have taken those antibodies and shown that they could be used as a cancer-detection test.

Mr. **Skeen**. Stay in there, Doctor, I think you're doing a fine job.

Dr. **Feller**. So—yeah.

Mr. **Gore**. When is the Feller technique——

Dr. **Feller**. Well——

[Laughter.]

Mr. **Gore** [continuing]. To be?

Dr. **Feller**. We are currently going to undergo the clinical studies. We have at this point studied about 70 women and we are detecting about 95 percent of all early breast cancer and we are starting our extended clinical studies perhaps in about 3 months.

Mr. **Gore**. Ninety percent?

Dr. **Feller**. Ninety percent. Pickup. Detection of early cancers.

Mr. **Gore**. Ninety percent detection.

Dr. **Feller**. That is our preliminary data. May I underline the word "preliminary." With all these distinguished scientists sitting here, I want to underline that these are very preliminary data.

Mr. **Skeen**. Did you hear heavy breathing over your shoulder there?

Dr. **Feller**. I think Dr. Temin here is breathing over my shoulder, right. [Laughter.]

Now, let me point out, Congressman, I want to follow that reasoning because the point is, as you've said, and Congressman Skeen has, early diagnosis is the key to cure. Now, I wanted to point out to you that with present day techniques, in 1984, if we were to apply mammography across the board to every woman over 50, we could raise the cure rate for breast cancer, the most common cancer, to 80 percent, and indeed, we have certain subgroups of women with breast cancer that we picked up in mammography that we are achieving 90 percent cure today.

So, again, I think that the key—now, you have selected the pancreas, but if you think of the pancreas and the breast, the accessibility to study is quite different and you see, we have no good methods for either feeling the pancreas or really x raying the pancreas.

So I think that when we talk about these 90 percent rates, we can probably achieve these with many of these forms of cancers. Now, again, I would—going back to Congressman Skeen—I don't think, Congressman, that if the oncogene research leads to these antigens that are useful, I don't think that the delay in developing these blood tests would be very long. I think, Congressman, as you know, this is a free-enterprise country and I think industry is obviously extremely interested in blood tests for breast cancer and there are a number of American companies, both new companies and the established companies, that would invest several million dollars and would help the academic centers bring these to the public.

I think, as Peter has said, with the AIDS test, I would suspect, wouldn't you, Peter, that we will have an AIDS test for blood transfusion products, what, in a year or so?

Dr. **Fischinger**. Six months.

Dr. **Feller**. Six months. So I think that once the scientific community has identified useful agents, I don't think the delay, Congressman Skeen, is a problem. Because of the commercial value of those tests, the private industry will step forward quite rapidly.

Mr. **Skeen**. If I might pursue that just a little bit—how's my time?

Mr. **Gore**. Fine.

Mr. **Skeen**. All right. For instance, Doctor, some years ago, I'm aware that they came up with a carcinoembryonic antigen blood test.

Dr. **Feller**. Right.

Mr. **Skeen**. Still, many laboratories, including the one here that the Members of Congress go to for their annual physicals, don't know what a CEA test is. Or they know what it is, but they're not that familiar with it, and it is amazing to me because it's a basic tool. And I am saying if the technique of oncology and the concept of doing this kind of diagnostic work, there is some kind of resistance somewhere along the line that because maybe it's a rarely used test or what is it?

Dr. **Feller**. Yes.

Mr. **Skeen**. Is it costly?

Dr. **Feller**. No, Congressman, the problem with the CEA test is its accuracy of pickup. I would point out that if you use CEA in a screening test, it would probably only pick up about 30 percent of early colon cancers and if one were to use it as a general cancer screen, I'm afraid that we would only pick up perhaps 20 or 25 percent of all cancers.

Mr. **Skeen**. The point I was trying to make, Doctor, was that it was an early technique.

Dr. **Feller**. Right, it was a very early technique, but it was shown that it only really detected in a relatively early stage, about 30 percent of colon cancers.

Mr. **Skeen**. Then I can understand why.

Dr. **Feller**. Yeah, now it is used, I want to say it is used very extensively throughout the country for recurrent cancer. Patients who do have colon cancer——

Mr. **Skeen**. You establish baseline with it.

Dr. **Feller** [continuing]. To establish baseline and we do use it clinically so that if a patient with colon cancer is monitored and then suddenly gets a high CEA, it is a very good test.

I think I want to say, Congressman, that the CEA test has shown the medical profession that blood tests do work, but the problem has been that they usually work only on the late cancers. That is why I think our work at Georgetown and Holland is very exciting because our blood test——

Mr. **Skeen**. I'm glad you put Georgetown first.

Dr. **Feller** [continuing]. Is picking up the early tests. I might say that we have one patient, Congressman, that had a cancer that was about a quarter of an inch, about four millimeters, and this was detected by the blood test. So again, I want to stress that I think many clinical cancer scientists are pinning our hopes for early diagnosis on blood tests.

Mr. **Skeen**. Thank you very much, Doctor. The reason I asked that question was that was my concern, that when you do develop and these concepts come up, sometimes there seems to be some kind of lag or resistance amongst the practitioners in using various kinds of tests. I think I just used the CEA as an example because it was an early tool, but I'm beginning to understand what the problem is and I have certainly appreciated—you've illuminated and expanded my field of understanding of this thing and I appreciate that very much.

Thank you, Mr. Chairman, that's all I have.

Mr. Gore. Well, thank you.

Now, again, we want to use this panel to try to put the whole thing into perspective and then we're going to move on to the next panel.

Back when I was in grade school, I read a book called "The Microbe Hunters," a very famous commonly read text in school, and everyone is familiar with the breakthrough in medicine which took place with the discovery of bacteria. Now, is it fair to draw an analogy between what the discovery of bacteria meant in combatting infection to what the discovery of oncogenes and proto-oncogenes will mean to the fight against cancer? With one caveat, to use Mr. Haig's word——

[Laughter.]

Mr. Gore [continuing]. When bacteria was discovered, we didn't have an infrastructure in place which enabled us to use that insight. With the discovery of oncogenes, we do have a medical infrastructure which allows the rapid and early exploitation of this insight to quickly and dramatically increase the survival rates for cancer.

Is the general analogy a valid one?

Dr. Feller. Yes, I believe it is. I believe that, as you've said, that the discovery of oncogene can be compared to the discovery of bacteria and I think you are right, that today we do have the infrastructure, we do have the very heavily invested into medical research laboratory and I think that with this infrastructure, the National Cancer Institute being the prime example of these very heavily endowed research institutions, that one can expect that the treatment strategies will evolve very much more rapidly.

I point out that going back to the tubercle bacillus, that remember, it was 60 years from 1880 to 1940 when the use of the antibiotic streptomycin came in, so that that 60 years—and that is going back 100 years—so that's why I don't really think, Congressman, that a 10-year goal of achieving some of these treatment strategies is unrealistic.

Mr. Gore. Well, that is very exciting stuff. Go ahead.

Dr. Fischinger. Let me say that I think in the recent past, our progress has really outstripped our projections on many, many cases.

Dr. Feller. Right.

Dr. Fischinger. One of the interesting things that I can give you are two classical examples. Sometimes we can do something about the disease even without knowing exactly what is happening. We can go all the way back to Louis Pasteur; he didn't know about the rabies being a virus, but he could actually make a vaccine a 100 years ago.

On the other hand, people have also discovered a penicillin. You knew it worked. You knew it had an effect; you didn't know how it worked for the next 25 years or so.

In other words, I think we're open; we're ready for all kinds of possible developments, but you are absolutely right, we have a great infrastructure in place. The modern biotechnology is opening new doors every day.

Mr. GORE. You know, we heard earlier the discussion of your conservative estimate and Dr. Feller's more optimistic estimate. You don't think that 90 percent by 2000 is unrealistic, do you?

Dr. FISCHINGER. Let me say this, that one of the elements that is really difficult to assess is human nature, that if people give up smoking, then I think that figure will be much closer in terms of realization. If they don't, we will have lung cancer continuing and lung cancer does not today have a very good prognosis.

So, many of these elements have to come into play to reach a magical figure like that.

Mr. GORE. Yes, all right. Now let me get a little better overview of this, OK? Specifically, what we're talking about is the discovery of the exact mechanism within the human cell which initiates the onset of cancer. Specifically, medical science has now identified genes, known as oncogenes, that preexist within the body and that are turned on so that they express the information they contain, causing uncontrolled growth. They are turned on, both by viral transfer of genetic information that triggers the onset of the mechanism and by environmental insult that, by a mechanism less well understood, also turns on this mechanism that causes uncontrolled growth.

Now, is that essentially it?

Dr. FISCHINGER. I would like to compliment you on your erudition and the background.

Mr. GORE. OK.

Dr. FISCHINGER. That is very well put.

Mr. GORE. All right——

Dr. FELLER. But, Congressman, could I add one fill-up there, and that is the word "exact." You know, as a scientist, we listen for every word and I would take a little bit exception——

Mr. GORE. Yeah.

Dr. FELLER [continuing]. When you said to discover the exact mechanism I think we have an outline, a very good outline, an overview of the mechanisms, but I think——

Mr. GORE. Yeah.

Dr. FELLER [continuing]. Dr. Temin would be the first to say here that if he goes back to his laboratory, we don't have the exact mechanism.

Mr. GORE. OK, so, to draw another analogy, if we were in the position of Christopher Columbus sailing to the new world, the lookout in the crow's nest has now told us that land is right there——

Dr. FELLER. That's right.

Mr. GORE [continuing]. And we're headed toward it——

Dr. FELLER. That's right.

Mr. GORE [continuing]. But we're not there yet——

Dr. FELLER. That is right.

Mr. GORE [continuing]. And many thousands of people will die before we get there who could be cured by the techniques we will have once we set foot on that other shore.

All right. Two quick questions: Are you familiar with Ronald Levy's work at the University of California, where he treated a patient with lymphoma with monoclonal antibodies, which treatment apparently resulted in complete remission? It has not been repeated.

Are you familiar with this and what is its significance?

Dr. **Fischinger**. We're very much familiar with it. We have been following this. As a matter of fact, Dr. Levy won the Armand Hammer prize because of this particular discovery. The interesting thing about it is that in that type of a lymph tumor, a lymphoma, you will have on its surface a very specific and a unique determinant which you can then make a monoclonal antibody to.

And then, when this monoclonal antibody was applied to that patient, it wiped out the tumor. The possibility of that tumor going away spontaneously was very remote under those conditions.

However, you are absolutely right that the next subsequent several patients that were treated with analogous monoclonal antibodies did not do so well. It might be that since those monoclonal antibodies were not armed, as I described before, that you may have to add some arming mechanism. You want to put on a poison on the monoclonal antibody or a radioactive tag to destroy the tumor more efficiently.

I think he was able to target onto the tumor cells, but the cells didn't die as well in the process.

Mr. **Gore**. OK.

Did you want to ask something else before we go on?

Mr. **Skeen**. No, Mr. Chairman, I just would like to say, in reference to your bill in on labeling on tobacco products——

Mr. **Gore**. Yeah.

Mr. **Skeen**. I don't know, but maybe these doctors or somebody could come up with a better, more graphic means because those folks with the warning labels are still——

Mr. **Gore**. Yeah.

Mr. **Skeen** [continuing]. Going to smoke those cigarettes. Maybe if you could put a picture of some lung tissue from a cadaver on the package, it might do more good than trying to read the warning. Just a thought.

Thank you, Mr. Chairman.

Mr. **Gore**. Just to follow up on that, this compromise has now passed the Energy and Commerce Committee 22 to nothing and will be scheduled for a vote on the floor very soon and it has the warnings on the advertisements and billboards 50 percent larger than the current ones and they're going to be rotated so that there are four separate warnings, much more strongly worded. And the rotation is designed to ensure that the warning doesn't just wear out like water off a duck's back, just do no good.

Combined with the educational program, we can hope that it will make a difference.

Why don't we go on to the next panel. Let me thank both of you for your help in getting us off to a good start with your overview. We really appreciate it. Thank you.

Dr. **Feller**. Thank you.

Mr. **Gore**. Let me call the next panel up now. Dr. Howard Temin, professor of viral oncology and cell biology at McCardle Laboratory at the University of Wisconsin; Dr. George Vande Woude, director of basic research programs at Litton-Bionetics Institute in Frederick, MD; Dr. Charles Sherr, chairman of the Division of Human Tumor Cell Biology at St. Jude's Children Hospital in Memphis; Dr. Stuart Aaronson, Chief of the Laboratory of Cellular and Molecular Biology at the National Institutes of Health of the National Cancer Institute in Bethesda.

If all four of you could come on up to the witness table. We're particularly delighted to have Dr. Howard Temin, who is a Nobel Prize winner; particularly delighted to have Dr. Charles Sherr, who is a Tennessean and both of our other witnesses who are helping us out today.

Mr. SKEEN. What State was that? [Laughter.]

Dr. SHERR. A transplant from Tennessee. [Laughter.]

Mr. SKEEN. Transplant. [Laughter.]

Mr. GORE. That's all right, Doctor, that's all right. We'd rather have you coming as going.

Without objection, all of your prepared statements will be included in full in the record. If you can summarize your presentations to get the heart of it across to us in a way we can understand it, we'd appreciate it and we will start, Dr. Temin, with you.

We're delighted to have you here and invite you to proceed.

STATEMENTS OF DR. HOWARD M. TEMIN, PROFESSOR OF VIRAL ONCOLOGY AND CELL BIOLOGY, McCARDLE LABORATORY, UNIVERSITY OF WISCONSIN; DR. GEORGE F. VANDE WOUDE, DIRECTOR OF BASIC RESEARCH PROGRAMS, LITTON-BIONETICS INSTITUTE, FREDERICK, MD; DR. CHARLES J. SHERR, CHAIRMAN, DIVISION OF HUMAN TUMOR CELL BIOLOGY, ST. JUDE'S CHILDREN HOSPITAL, MEMPHIS, TN; DR. STUART A. AARONSON, CHIEF, LABORATORY OF CELLULAR AND MOLECULAR BIOLOGY, NATIONAL INSTITUTES OF HEALTH, NATIONAL CANCER INSITUTE, BETHESDA, MD

Dr. TEMIN. Thank you. I appreciate the opportunity of appearing here today and communicating some of the progress we've recently made in cancer research. I should say that I am very impressed with the amount you already know about it.

What I'm going to do, as a professor, is just go away from the future projections and I, and the rest of the panel, are going to tell you about the scientific background of what we know now, which is the basis for some of these very optimistic, I think, projections.

In terms of your analogy, you should remember that when Columbus' lookout sighted land, it wasn't the continent; it was an island——

Mr. GORE. Yes.

Dr. TEMIN [continuing]. In front of the continent——

Mr. GORE. Yeah.

Dr. TEMIN [continuing]. And I think that may be a better way to look at your analogy——

Mr. GORE. And he thought it was India. [Laughter.]

Dr. TEMIN. That's right, that's right.

Mr. SKEEN. You folks are great on literalization, I'll tell you. [Laughter.]

Dr. TEMIN. In terms of the other analogy with bacteria, you must remember that we know the causes of lots of diseases, virus diseases, colds and so forth without having therapies, so that understanding does not necessarily lead to control, unfortunately. We wish that it could be.

The example of AIDS is a little misleading in respect to cancer. AIDS HTLV appears to be a virus which spreads by ways we hope that are similar to ways we knew before. It puts the disease in the class of disease we know how to handle and test for. Now oncogene research, which we'll describe in the case of this disease is a different kind of disease. We don't have models so a prediction tells you something about the person making the prediction. We just don't know because this is a new kind of disease for us to attempt to deal with.

So now, when we think about the causes of cancer, as you've discussed, we think primarily of smoking, and I want to second your concern with smoking because stopping that would be more than any of the fruits of oncogene research. If we could stop cigarette smoking in this country, we could reduce cancer mortality by 40 percent. So that would be the single most important thing we could do.

We don't think much about viruses in cancer in this country because viruses are not important in this country. They are important in places like China where primary liver cancer is a primary cause of death and that is caused by virus and may be able to be prevented by prevention treatments that are used with virus infections.

But viruses are important because they cause cancer in animals in a very simple fashion and if I could have the first slide, just to indicate——

[Slide.]

Dr. Temin [continuing]. This is just to show an example of a virus that causes a cancer in an animal. Where there should be two chickens, and one of them was injected 2 weeks earlier with the virus which causes cancer.

The chicken on the left is alive and the chicken on the right, with the virus, is killed in 2 weeks with a fulminating cancer. That is what these viruses can do. Fortunately, there are no viruses like this in people.

The next slide——

[Slide.]

Dr. Temin [continuing]. Shows another example of a virus which causes a tumor in tissue culture. This is the famous Rous sarcoma virus, which causes that little focus, we call it, and it's because of the ability to see things like that in culture we could find out so much about these viruses.

Now, to understand how these viruses cause cancer, we need to review a little biology. The next slide——

[Slide.]

Dr. Temin [continuing]. Just shows you a cell with the three major informational molecules: the DNA making the RNA making the protein; the cell divides giving a new cell. Again, DNA, RNA, and protein.

The cancer-causing viruses that we've mentioned today already that led to the discovery of oncogenes—the next slide——

[Slide.]

Dr. TEMIN [continuing]. Are different. They reverse the usual flow of information. Instead of going DNA, RNA, protein; they go RNA, DNA and then DNA, RNA, protein——

Mr. GORE. These are the retroviruses——

Dr. TEMIN. And they're called retro because they reverse the process. Instead of going from DNA to RNA, they go from RNA to DNA.

Mr. GORE. Again, if I could use an analogy to help my own understanding of this, for anyone who's used a small computer, you typically will have a master copy and then you'll run off copies that you use in the course of everyday work. And in that model, the DNA would be your master copy and it'll run off RNA——

Dr. TEMIN. I think, to make the example better, if you had your master copy on a hard disk——

Mr. GORE. OK.

Dr. TEMIN [continuing]. And then you made your copy on a floppy diskette——

Mr. GORE. And that would be the RNA.

Dr. TEMIN. That would be the RNA.

Mr. GORE. OK, and in a retrovirus——

Dr. TEMIN. And a retrovirus——

Mr. GORE [continuing]. You take the information that's on the floppy disk——

Dr. TEMIN. And put it——

Mr. GORE [continuing]. And get it back on and printed onto——

Dr. TEMIN. The hard disk.

Mr. GORE [continuing]. The hard disk, all right.

Dr. TEMIN. It's a very good analogy. And just to make the point clear, the next slide——

[Slide.]

Dr. TEMIN [continuing]. This differs from the normal RNA viruses which are the things that cause colds and influenza and just go and replicate through RNA and don't involve DNA at all. So retroviruses are a special kind of virus.

Now, if we look at the retrovirus, the next slide——

[Slide.]

Dr. TEMIN [continuing]. We can look at the retrovirus as a string, or we speak of it as a sequence, or you could think of it as a sentence of information that goes along and has at the ends repeated sequences shown as those boxes which control what the virus is going to do, and in the inside, there is the information which controls the viral protein.

Now, if you look at the bottom, we have the viruses that cause those cancers you saw, and you see at the ends they are the same. They have the same information that control the virus replication, but in the middle, they have that block there, and that block is called the oncogene because that block codes for a new protein and genetic experiments show that the protein coded for by that block causes the cancer, and that led to the discovery and the definition of oncogenes.

Now, this research started 70 years ago with Rous sarcoma virus; then about 25 years ago, with the idea of a cancer gene in the virus; and in the last 10 years, the next slide——

[Slide.]

Dr. **Temin** [continuing]. We've seen the identification of lots of oncogenes and we know that the way, then, that these viruses cause cancer is that the virus with the oncogene infects a normal cell and because it is a retrovirus, it can put the cancer gene into the normal cell DNA, as shown at the bottom, and there the oncogene makes the normal cell a cancer cell.

So this is a special thing that a retrovirus can do that other viruses can't do; it can take from the outside of the cell the cancer gene and add it into the cell, and that cancer gene makes the cell tumorous.

The next slide.

[Slide.]

Dr. **Temin**. Now we know about—it's too small for you to see. You have a list of them in the handout. Lots of different oncogenes. Now, these have different names. The important thing is it's not an infinite list. We've discovered about 20 different oncogenes, one or two new ones are being discovered every couple of months, but it doesn't appear that there are an infinite number of oncogenes.

Mr. **Gore**. There are about 20 you know of now and there are probably——

Dr. **Temin**. That's right.

Mr. **Gore** [continuing]. In the range of double that when you——

Dr. **Temin**. That would be a fair guess and we guess that it's only double because when we discover new ones, they turn out to be like ones we already knew. So it may be that there's only a small, relatively small number. There may be of the order of 50,000 total genes in the cell. It's only maybe 0.1 percent of them that may be related in this way to cancer.

Now, we've discovered—the next slide——

[Slide.]

Dr. **Temin** [continuing]. That the oncogenes come from normal genes called proto-oncogenes, "proto" because they're precursors, and you see what happens is the retrovirus on the left goes into a cell and somehow, by a process of normal genetic engineering, the retrovirus captures part of that cell's gene, so you see directly there that the oncogene comes from the normal cell gene, but you also see there, in the next slide——

[Slide.]

Dr. **Temin** [continuing]. We'll just list that the oncogene and the proto-oncogene are not exactly the same. The oncogene differs by having some different amino acids. The amino acids are the building blocks of the proteins.

Mr. **Gore**. Wait a minute, could you go back to that——

Dr. **Temin**. Go back.

Mr. **Gore** [continuing]. Last slide and clear up for me——

Dr. **Temin**. Yes.

Mr. **Gore**. [continuing]. The relationship between oncogene and a proto-oncogene.

Dr. **Temin**. All right. Now, what we have in the normal cell—forget now the retrovirus——

Mr. **Gore**. Where is the normal cell?

Dr. **Temin**. The normal cell—imagine the top line without the retrovirus.

Mr. **Gore**. All right.

Dr. TEMIN. All right, the proto-oncogene—and there're approximately 20 to 40 of these——

Mr. GORE. Yeah.

Dr. TEMIN [continuing]. Is a normal cell gene——

Mr. GORE. Uh-huh.

Dr. TEMIN [continuing]. And I've drawn that way because normal cell genes are not continuous, but have things in between we call introns or intervening sequences. All right. Now, this is a gene which is—Dr. Aaronson and Dr. Sherr will tell you—has an important normal cell function. We all have a proto-oncogenes; none of us have cancer——

Mr. GORE. We don't know what that function is yet, though.

Dr. TEMIN. We know some cases. We'll tell you those things.

Mr. GORE. OK.

Dr. TEMIN. Now, what happens in the case of the viruses that we're talking about is the virus goes into a cell and adds its DNA to the cell DNA so you see there the retrovirus shown by the two boxes is sitting next to the proto-oncogene. We still have a normal cell.

But then, by a process of genetic engineering, the retrovirus picks up the proto-oncogene and puts it in its middle and so now, we have——

Mr. GORE. What's it in, the middle of, the virus?

Dr. TEMIN. Of the virus.

Mr. GORE. OK.

Dr. TEMIN. It puts it in the middle of the virus and so now we have a new virus, a virus that is, on the one hand, formed from a virus, and on the other hand, formed from a part of the cell DNA.

Mr. GORE. Proto-oncogene, yeah.

Dr. TEMIN. The proto-oncogene, and these have been put together, and it is in the process of putting them together, that the proto-oncogene has been made different. So that's the important thing, that——

Mr. GORE. Well, now, wait a minute. You've got the proto-oncogene——

Dr. TEMIN. Yes.

Mr. GORE [continuing]. In the normal cell——

Dr. TEMIN. Yes.

Mr. GORE [continuing]. The virus comes——

Dr. TEMIN. In.

Mr. GORE [continuing]. In and takes a little slice of information——

Dr. TEMIN. That's right.

Mr. GORE [continuing]. Out of the proto-oncogene——

Dr. TEMIN. Out of the cell, yes.

Mr. GORE. All right, now, the subtraction. Now, the virus then goes——

Dr. TEMIN. Then the virus—the virus then can go—the virus information—it makes RNA—goes and infects other cells and still remains in the first cell.

Mr. GORE. And still remains in the first cell.

Dr. TEMIN. Yes.

Mr. GORE. OK. Now, in both cases, the virus, plus the new information bits from the proto-oncogene, is that what you're calling an oncogene, the virus plus that information, or are you calling the proto-oncogene plus the viral-induced chain?

Dr. **Temin**. OK, Congressman, you're extremely acute. [Laughter.]

I must say, this is something which the field has not decided and most people don't very carefully make the distinction you're trying to make. I think we call the oncogene—people use the term both ways—but I think primarily we talk about the oncogene as the part taken from the proto-oncogene that's put into the virus. But either—both ways are used in the literature.

Mr. **Gore**. OK. All right, and in both cases, the sequence of the information has been rearranged.

Dr. **Temin**. Has been changed.

Mr. **Gore**. Changed.

Dr. **Temin**. Changed, that's right, and the next slide will indicate the nature of these changes——

[Slide.]

Dr. **Temin** [continuing]. Some of the changes, as Dr. Aaronson will mention, is a difference in the building block of the protein. Other changes, as Dr. Vande Woude will mention, are that the controlling sequences are different so that the oncogene is expressed where the proto-oncogene is not expressed. And other changes are that the proto-oncogene in the virus is then moved to different locations in the cell, as again, Dr. Vande Woude will talk about.

So by these means of genetic evolution, natural genetic engineering has mutated in these senses a normal gene to make it a cancer gene.

Mr. **Gore**. Uh-huh.

Dr. **Temin**. All right, so the next slide——

[Slide.]

Dr. **Temin** [continuing]. So we conclude, then, how these viruses work—that highly oncogenic viruses—retroviruses cause cancer by adding to the DNA of normal cells at new locations a multiple altered or mutated cell gene. So this is something we now understand.

Now, this is understanding in genetic terms. The really important question, as far as therapy, is how in biochemical terms the altered genes work, and here, unfortunately, we don't understand. This is something we're going to have to learn. What we do know—the next slide——

[Slide.]

Dr. **Temin** [continuing]. Is something about how the proto-oncogenes work and the proto-oncogenes work as making growth factors or receptors for growth factors—this is in chart 5 of the handout—or as cell structural proteins or cell cycle proteins.

In other words, the proto-oncogenes, the normal cell genes, are involved in normal cell growth and so what we think may be important—the next one on the back——

Mr. **Gore**. Yeah.

Dr. **Temin** [continuing]. And so what we think may be important then is that when they're altered in the virus, then they're involved in abnormal cell growth. But so far, we've been unable to prove that. This is the hypothesis.

Now, up until a very few number of years ago, this work was what we call basic research, in that it was relevant to animal cancers; it was not relevant to human cancer, but that changed with the discovery that the same genes, the same proto-oncogenes—the next slide——

[Slide.]

Dr. TEMIN [continuing]. Were altered in some human cancers. So now we know some of these same genes, the H-RAS gene, is altered in bladder cancer. The K-RAS gene is altered in bladder, colon, gall bladder, lung, pancreas carcinomas and in sarcomas. The MYC gene is altered in Burkitt's lymphoma and neuroblastoma, and the ABL gene is altered in chronic myelogenous leukemia, so the same genes that we found in viruses causing cancers in animals are now found to be altered in human cancers.

We assume, but we have not proven, that, therefore, these genes are involved in causing the cancer or in the progression of the cancer. Now, that is, again, a leap from our knowledge that they cause cancer in animals, that, therefore, when they're present in the human cancers in an altered form, that they are related to the cancer. That's very likely.

So basic cancer research with viruses has thus proved directly relevant to human cancer by identifying genes which can lead to cancer when several of them are altered in one cell.

The last slide——

[Slide.]

Dr. TEMIN [continuing]. Is just to indicate that in the case of the virus, the virus can, in one step, cause cancer by introducing the multiply altered cell gene, but at the bottom, in the case of human cancers and nonviral cancers, we need at least three and maybe more changes so it's an accumulation of different changes. I've shown one as a mutation, one as an amplification, another as a translocation. This is hypothetical, but the virus is a simple model.

In the human cancer, we have a more complicated thing that leads to the same result, the alteration of normal genes leading to cancer.

Thank you.

[The prepared statement of Dr. Temin follows:]

Testimony of Howard M. Temin, McArdle Laboratory, University of Wisconsin, Madison, Wisconsin 53706 before the Subcommittee on Investigations and Oversight of the U.S. House of Representatives Committee on Science and Technology hearings on the Status and Implications of Oncogene Research, June 6, 1984.

ONCOGENES

I am Howard Temin, American Cancer Society Research Professor at the University of Wisconsin-Madison. I appreciate the opportunity of appearing before you today to communicate some of the progress made recently in cancer research. This progress results from the knowledge gained as a consequence of the increased support of cancer research and of the availability of the techniques of genetic engineering.

When we think of the causes of human cancer in the U.S., we think of smoking, x-rays, asbestos, and other chemicals. In addition, we are now aware of other environmental factors, including different lifestyles, which affect cancer incidence. It is only rarely in this country that we think of viruses causing human cancer. Viruses are not an important cause of human cancer in the United States, although in some parts of the world virus-caused cancers are important. For example, liver cancer, a major cancer in China and other less developed parts of the world, is probably caused by a DNA virus, called hepatitis B virus.

Although viruses cause only a small fraction of human cancer, there has been enormous attention paid to viruses by people interested in the causes of cancer. This is because some viruses cause cancer in a relatively simple fashion. Viruses, thus, have been used to identify genes that lead to cancer, the so-called cancer genes or oncogenes.

One of these viruses, named Rous sarcoma virus, causes tumors of the connective tissue in sensitive chickens within a week or two, and another virus, reticuloendotheliosis virus strain T, causes leukemia and death of chickens within two weeks.

To understand how these viruses cause cancer, we need to review a little basic biology. Normally in the cell there is information flow from genes in the master chemical, DNA, to the messenger chemical, RNA, to the proteins which form the actual building blocks and machinery of the cell.

The cancer-causing viruses we are interested in today are different from usual RNA viruses. They are called retroviruses because they reverse the usual flow of information in the cell. Retroviruses themselves contain RNA, the usual messenger chemical, as their genetic material. However, upon infection of a cell retroviruses reverse the usual flow of genetic information from DNA to RNA and transfer their genetic information from RNA to DNA. They then add their DNA to the cell DNA where it forms a stable part of the cell genetic material. In contrast, the usual RNA viruses do not transfer information to DNA.

The genetic information of a retrovirus is a string or sequence which is divided into two parts, the ends and the middle (Chart 1, top). The sequences at the ends are repeated and contain the information that controls when and how the virus replicates. In the middle is the information that codes for viral proteins. Retroviruses that cause cancer rapidly are distinctive compared to other retroviruses. In the case of these highly oncogenic retroviruses, the ends of the virus are not different (Chart 1, bottom). However, the middle of the virus is changed so that instead of coding for viral proteins it codes for some new proteins. Genetic experiments show that these new proteins cause cancer. Thus, the genes coding for the new proteins are called the viral oncogenes or cancer genes. Highly oncogenic viruses cause cancer rapidly and efficiently because they add a cancer gene to the cell DNA (Chart 2).

Highly oncogenic retroviruses were first described over 70 years ago by Peyton Rous. A chicken fancier brought him a chicken with a tumor. In transplanting this tumor he discovered the virus, Rous sarcoma virus, which was critical in unfolding the story I have just told. Basic research on this chicken virus lead to the discovery of oncogenes. This research started about 25 years ago with mutants of Rous sarcoma virus that began to define the viral oncogene. Nucleic acid hybridization and recombinant DNA experiments in the last ten years completed the definition. At the present time we know about 20 different viral oncogenes (Chart 3, Appendix I). These oncogenes are named according to the virus they were found in and separated into different families depending upon the type of protein they make and their genetic relatedness.

Oncogenes evolved from normal cell genes called proto-oncogenes. By a complicated process of natural genetic engineering and evolution, a normal cell gene is changed into a viral oncogene (Chart 4, Appendix I). This evolution changes the protein made by the altered proto-oncogene from the one produced by the normal proto-oncogene. These changes include mutations in the building blocks (amino acids) of the protein and/or changes in the information controlling when and how much of the protein is made. In addition, the process of infection by a highly oncogenic virus carrying an oncogene leads to insertion of the oncogene into a different location in the cell DNA. This different location allows the oncogene to escape from any regional controls affecting its expression.

Thus, we conclude that a highly oncogenic retrovirus causes cancer by introducing into the cell DNA a multiply altered cell gene.

Although we do not know in biochemical terms how the protein made by an oncogene causes cancer, in a few cases we know what the related proto-oncogene in the normal cell does (Chart 5). In these cases, the normal cell genes are involved in making factors for cell growth and cell division. Thus, the cancer genes in retroviruses appear to be altered cell genes controlling cell growth and division.

Up until a few years ago, this work was quite theoretical, of interest only to those concerned with basic cancer research. Although we who did this research always thought that it would be relevant to human cancer, it was not until a few years ago that it was demonstrated that in about one quarter of human cancers proto-oncogenes are altered. Examples of these alterations include an amino acid change in the ras gene in a bladder cancer, moving to new chromosomal locations a myc gene and the abl gene in different leukemias.

Thus, basic cancer research with viruses has proved directly relevant to human cancers by identifying genes which can lead to cancer when several of them are altered in one cell. This identification provides targets for therapy and means for diagnosis and perhaps prevention.

CHARTS

Chart 1. (Top) DNA of a replicating retrovirus. The open boxes are the long terminal repeats and the line is the viral coding sequences. (Bottom) DNA of a highly oncogenic retrovirus. The slashed box is the oncogene which is substituted for some viral coding sequences. Other symbols are as in the top figure.

Chart 2. Cancer formation by a highly oncogenic retrovirus. A normal cell with nucleus and the DNA of a highly oncogenic retrovirus are shown at the top. When the highly oncogenic retrovirus infects the normal cell it adds its DNA to the cell nuclear DNA and transforms the infected cell to a cancer cell.

Chart 3. List of viral oncogenes, the species from which they were isolated, and how they are grouped.

Chart 4. Formation of a highly oncogenic retrovirus from a replicating retrovirus and a normal cell gene. At the top is shown a retrovirus inserted into the DNA of a cell near a normal cell gene. At the bottom is shown the DNA of a highly oncogenic retrovirus. Symbols are as in Chart 1.

Chart 5. Functions of some proto-oncogenes.

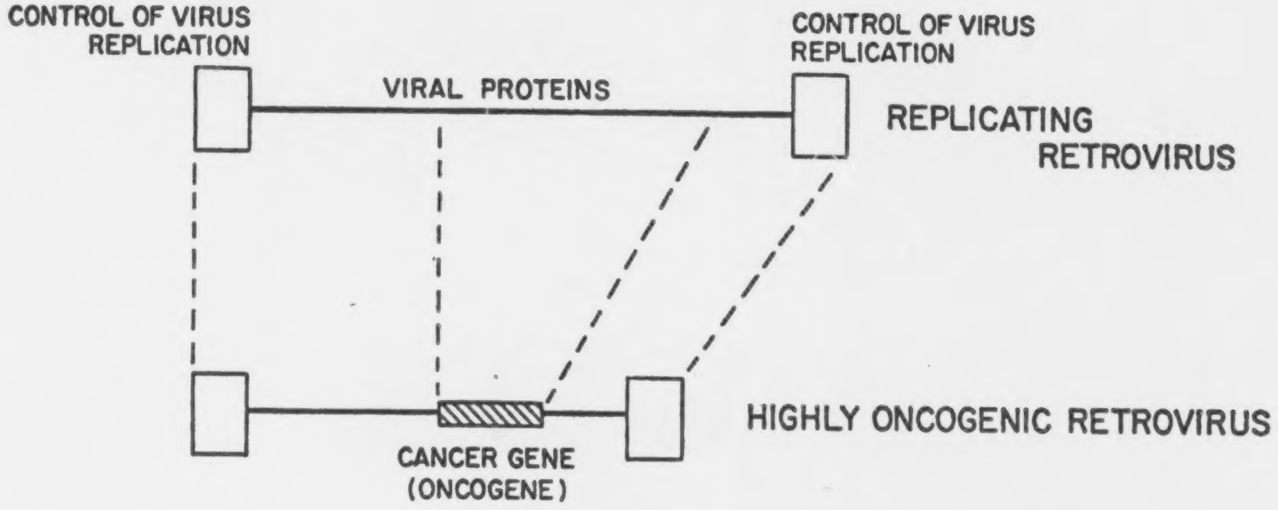
CONTROL OF VIRUS REPLICATION
VIRAL PROTEINS
CONTROL OF VIRUS REPLICATION
REPLICATING RETROVIRUS
CANCER GENE (ONCOGENE)
HIGHLY ONCOGENIC RETROVIRUS

Chart I

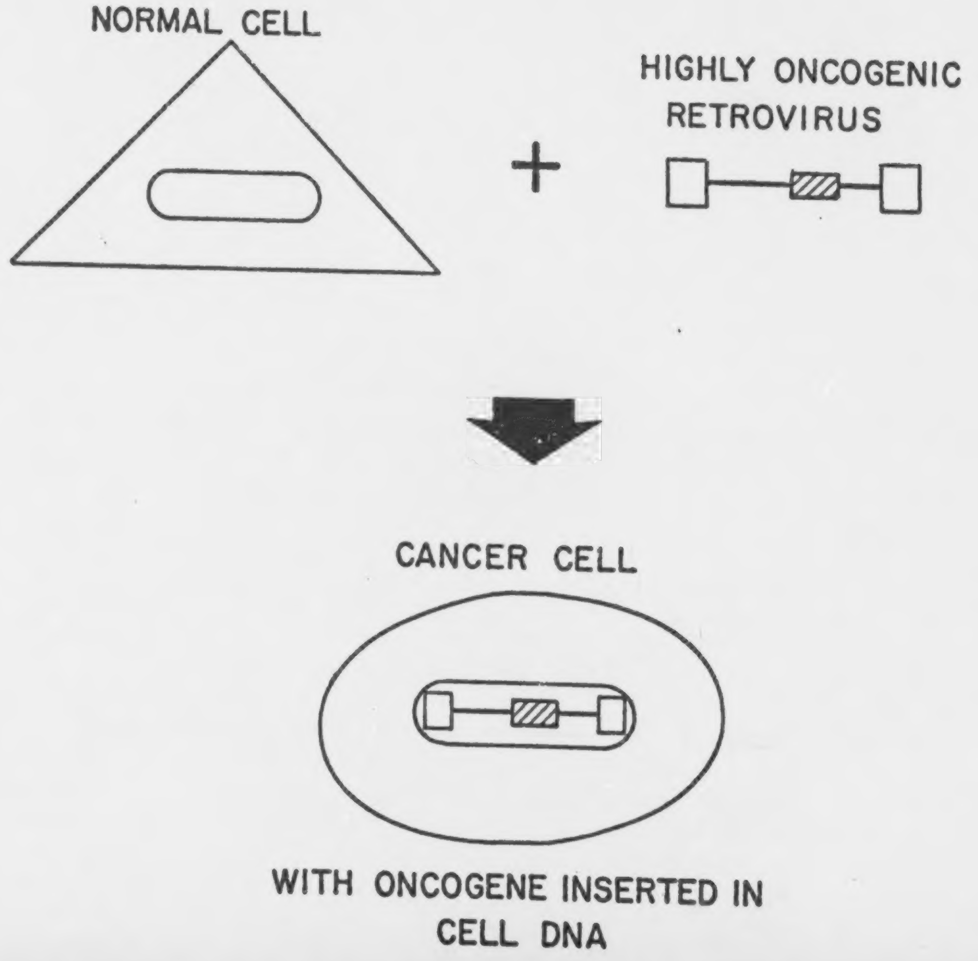
NORMAL CELL
+
HIGHLY ONCOGENIC RETROVIRUS
CANCER CELL
WITH ONCOGENE INSERTED IN CELL DNA

Chart 2

VIRAL ONCOGENES	SPECIES OF ORIGIN	CLASSIFICATION
src	CHICKEN	TYROSINE PROTEIN KINASE ACTIVITY
yes	CHICKEN	
fps/fes	CHICKEN / CAT	
abl	MOUSE	
ros	CHICKEN	
fgr	CAT	
erb-B	CHICKEN	SEQUENCE RELATED TO *src*
fms	CAT	
mos	MOUSE	
H-*ras*	MOUSE / RAT	GTP BINDING ACTIVITY
K-*ras*	RAT	
myc	CHICKEN / CAT	NUCLEAR LOCATION
myb	CHICKEN	
fos	MOUSE	
raf/mil	MOUSE / CHICKEN	
ski	CHICKEN	
rel	TURKEY	
sis	MONKEY / CAT	

Chart 3

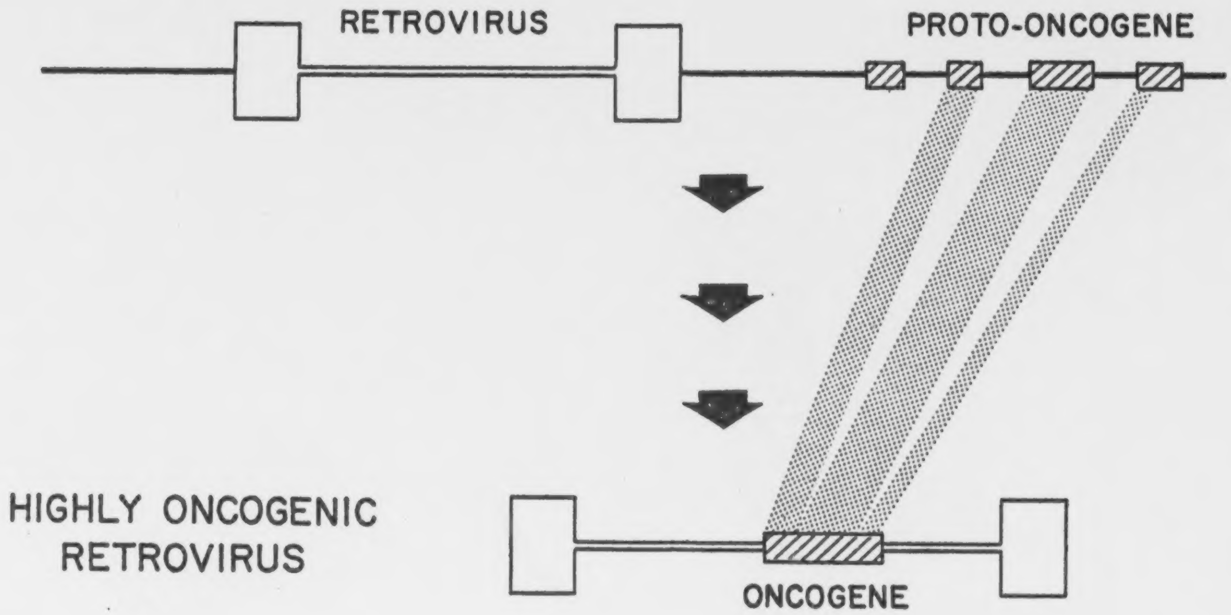
RETROVIRUS
PROTO-ONCOGENE
HIGHLY ONCOGENIC RETROVIRUS
ONCOGENE

Chart 4

VIRAL ONCOGENE	RELATED TO THE GENE FOR A
sis	GROWTH FACTOR
erb-B	RECEPTOR FOR GROWTH FACTOR
fgr	CELL STRUCTURAL PROTEIN
myc *src*	CELL CYCLE PROTEIN

Chart 5

Mr. GORE. Well, thank you very much.

Now, who should we go to next? Do you all have a preference?

Dr. TEMIN. Yes, Dr. Vande Woude will go next.

Mr. GORE. Dr. Vande Woude, we're delighted to have you here and please proceed.

Dr. VANDE WOUDE. Mr. Chairman, members of the subcommittee, it's a privilege to be here to testify at this hearing.

Mr. GORE. Could you——

Dr. VANDE WOUDE. Use this microphone?

Mr. GORE. Yeah, and maybe that one, too, yeah. Good.

Dr. VANDE WOUDE. What I would like to do, which may be a little elementary and I apologize if it is too elementary, but——

Mr. GORE. Don't worry about that.

Dr. VANDE WOUDE. OK. To describe what we feel is the basic elements that are involved in oncogene activation, so I'll be talking about the—some of the models that we've developed for activating an oncogene. I think the first—the use of proto-oncogene, the reason that there is some ambiguity in how it's used is because it's misleading in the sense that it says that the primary purpose of this gene in the cell is to promote transformation and I think quite contrary—although we have no solid evidence how they perform and descriptions of their precise functions, but nature has accepted the risk of keeping these oncogenes because they have an absolute requirement for them in the normal cell processes. So the potential for activation as an oncogene to cause cancer is probably required or necessary because they perform such important fundamental functions in the cell. And I'd like to address that by beginning with some simple models of genetic information; how it's transmitted in cells, and the first slide, I think——

[Slide.]

Dr. VANDE WOUDE [continuing]. Just shows a simple diagram, picture, cartoon of a normal cell with a nucleus and all of the genetic information that is responsible for determining what that cell does and how it functions is confined to the DNA molecule present in the nucleus and the next slide——

[Slide.]

Dr. VANDE WOUDE [continuing]. Shows that the DNA is actually dispersed in the cell, except at a very precise time in its cell division. If it was possible to have the DNA all hooked up as a single long tape and to grab the ends of this tape, it would measure a meter in length. Now, there are over a trillion cells in the body and each cell contains two copies of a DNA tape, actually, and if you think of a tape as you think of a tape in a cassette, in an audio cassette, all the information encoded for the function of that particular cell in that species, in the cell in that animal, all of the information for the cell to perform its function as a liver cell or as a lung cell or as a blood cell, is encoded in the genes that are part of that DNA tape.

Now, using the example of the audio tape—and I think the next slides shows this.

[Slide.]

Dr. VANDE WOUDE. So, from this cell that's less than one-thousandth to ten-thousandths of an inch in diameter, we can have a single DNA tape present in that cell that is responsible for all the genetic functions that cell performs as part of a tissue or organ that go to make up the whole body. It's differential expression of these genes that are encoded in this tape, so in the analogy where you have—would have a medley of musical pieces encoded in an audio tape, you are only expressing some of these songs, or you're only——

Mr. GORE. A refrain.

Dr. VANDE WOUDE. Right. Only a portion of the total number of songs that are encoded are being expressed in any one cell, and it's that differential expression which gives rise to the differential function of each cell.

Now, the presentation here as a long DNA molecule is incorrect. Actually, in the cell, the DNA tape is divided up into about 23 fragments. Each fragment is 4 or 5 centimeters long and just to give you an idea of the 4 or 5 centimeters long, the diameter of the DNA tape, if it was enlarged so that it would match the diameter of a tape in a tape cassette, which is a few millimeters, would be 100 miles long then. So that enlargement gives you the actual size comparison to what we use for recording information.

Thinking of it in the other direction, if you were to take a tape this long, this diameter, 100 miles long, and condense it down so that it was 5 centimeters in length, you would have all of the information of one twenty-third of the genetic information of the cell encoded in that little segment. So it's rather awesome what nature has—has contrived in order to contain these genetic functions.

There are 2,000 such genes, 2 to 5,000 such genes on each one of these segments, and obviously, in a cell, the linear form of the DNA tape could not be handled because the diameter of the cell is much too small, so the DNA tape is condensed into bundles. There are 23 such bundles and we refer to them as chromosomes. You can actually now begin to identify genetic functions that are on the specific bundles. Cytogeneticists have been able to distinguish the individual bundles by their structure, so in the cell, at a certain time during cell division, all of the DNA is condensed into these bundles and you can visualize individual bundles.

The genetic information in each unique bundle, or the genetic information in each bundle is unique and consists of between 2 and 5,000 genes.

What has this to do with oncogenes? Well, we've talked about 20 such oncogenes have been identified and they are randomly dispersed in this DNA tape so that you can—we have begun to identify where they are in the chomosome bundles and the next slide shows——

[Slide.]

Dr. VANDE WOUDE. Can we go on to the next one? I think that is out of order.

[Slide.]

Dr. VANDE WOUDE. OK—shows pictures of certain human chromosomes to which oncogenes have been the position of oncogenes in the chromosome has been identified, so of the 23 chromosomes, 8 are identified here and positions of some of the oncogenes that Dr. Temin had in earlier slides now are associated in those particular loci in the chromosomes.

Well, what impact did this have on our understanding of human disease? It had been known from studies for a number of years, more than 20 years, by cytogeneticists, that certain chromosomal rearrangements occur during—that are characteristic of certain human diseases. The example I'll use is in Burkitt's lymphoma. It was known for many years that in Burkitt's lymphoma, every cell Karyotype, or every chromosome analysis showed that chromosome No. 8 was rearranged and this we refer to as nonrandom rearrangement because every tumor always had a rearrangement involving this locus.

The importance of this is—it provided the cytogeneticists with a routine or common diagnostic tool for identification or absolute identification of the tumor, but when we began to look at these breaks at the molecular level, looking at the DNA level, we discovered something quite different, and I have to go back to the previous slide now if I can——

[Slide.]

Dr. Vande Woude. What we know from molecular analysis is that in the DNA—each gene consists of really two elements: One a regulatory element, which is responsible for the expression of the gene, a switch, if you will; and the second element, which is responsible for making the product, the protein. And it is the regulation of the switch which determines in which cell type the gene is expressed and the regulation of the switch, how much of the gene is expressed.

In many—as I described earlier, many individual cells of tissues or cell types, individual cell types, only certain classes of genes are turned on. Not all 50,000 genes are turned on; perhaps only 10,000. And what regulates that, which genes are turned on, is the switch.

Now, we know a lot about switches. We're not so clear on what regulates which switches are on in which cells, but for example, in Burkitt's lymphoma, it's a disease of blood cells that are responsible for producing antibody and we know that as those cells are derived from parental cells, we refer to that as terminally differentiate—they cease dividing—and as they slow down in their division rate, the amount of protein of the antibody type increases tremendously so that their sole function at the end, when they cease to divide, is to produce antibodies at high levels.

Now, the antibody gene has a regulatory element, a switch, which is turned on full blast, if you will, at the end of this differentiation process, but the cell has ceased to divide. And what we've learned is that as—as will be shown in the next few slides, is that that switch gets translocated in this chromosomal break so that it's placed next to an oncogene.

[Slide.]

Dr. Vande Woude. This is just a simple diagram of how normal cell genes may be displayed in the DNA tape. We show an oncogene switch. In this case, would be a proto-oncogene. It has its normal regulatory switch which precisely regulates the amount of oncogene expressed.

During cell division, at some—there's an error that occurs, and we're not quite sure how these errors do occur, except that the duplication of the DNA tape during cell division is not absolutely free of errors. It has a built-in error rate. At some frequency, an error is made and the next slide shows that——

[Slide.]

Dr. **Vande Woude** [continuing]. What can happen—if we can go to the next slide——

[Slide.]

Dr. **Vande Woude** [continuing]. During the duplication of the DNA tape, the rare change in the linear form of the DNA tape occurs which places the switch from an immunoglobulin gene—and the next slide——

[Slide.]

Dr. **Vande Woude** [continuing]. The switch from an immunoglobulin gene, which is the switch turning on the production of antibody next to the oncogene, and now the oncogene's regulation is overriddened by the switch from the immunoglobulin gene. The immunoglobulin is being made at high levels in a terminally differentiated cell. The cell is not supposed to divide.

That switch now, being transferred next to the oncogene, tells the oncogene to express product. The cell that's normally quiescent, not dividing, as a result of the oncogene being activated, can allow the cell to grow and proliferate and expand, and that, in itself, can account for some form of cancer as we know it.

Now, this translocation—it's referred to as a translocation. What happens is a segment of one chromosome translocates with a segment of another chromosome? The process is a selection process. This kind of translocation may go on at a very high frequency, but the only time we see the event is when the translocation involves activation of an oncogene and that's a selective process, the selective process being production of a tumor.

Now, the same oncogenes that we visualize in the cell were the oncogenes that Dr. Temin described earlier, that were captured by retroviruses. It is now known that the same kind of disease in birds, the activation of this particular oncogene, which is the myc oncogene in Burkitt's lymphoma, the activation by a viral switch proceeds through an analogous mechanism.

The next slide——

[Slide.]

Dr. **Vande Woude** [continuing]. The next slide again, please.

[Slide.]

Dr. **Vande Woude**. Dr. Temin showed you that the retrovirus has a switch which regulates its expression when it inserts into the DNA tape—the retrovirus inserts into the DNA tape by breaking the tape, opening it up, and inserting the virus into a position in the DNA tape.

When it does that, it takes it own switch in with it so it wants to make sure that it is expressed; it's not going to rely on the cell's switches to be expressed. It has it's own regulatory switch.

These switches, we found, will activate the expression of oncogenes, and so what we've done there is equate a genetic or a virus event with a genetic insult event. What we——

Mr. **Gore**. Hot-wired the gene.

Dr. **Vande Woude**. Hot-wired the gene, all right.

So it's now clear that there are a number of other ways that oncogenes can be activated. Dr. Aaronson and Dr. Sherr will describe those, but the last slide shows——

[Slide.]

Dr. VANDE WOUDE [continuing]. The number of ways we've identified oncogenes to be activated. Many of them involve increase—either deregulation of the expression of an oncogene, loss of the normal switch regulation, or gene amplification. This is a process where a segment of the DNA tape containing that oncogene is amplified to very high levels. Instead of there being one single copy of the gene in the cell, there may be 20 or 50, but it's not known what mechanisms activate that gene amplification, but the result is the same. Instead of having a low level of the gene, oncogene product, there are now many copies producing many molecules of the gene product and that oncogene product can lead to cell proliferation and growth in cancer.

The number of individual subjects that I've tried to cover are—promoter insertion is mechanism where the virus inserts its switch next to the oncogene. The chromosomal rearrangement is a characteristic that has now been associated with several different kinds of cancers and involve oncogene loci. By knowing now that when a cytogeneticist sees a nonrandom chromosomal translocation associated with a specific disease. that the breakpoints in the DNA tape are involving an oncogene in some kind of switch, we can now, even without knowing what the oncogene is, perhaps not even knowing what the switch gene is, go in and start pinpointing what that locus is, get the locus out and begin to identify the elements that are involved.

Dr. Aaronson, I think, will talk about single-point mutations in a gene, that is, the change of a single musical note in a recorded song, which makes it go from music to noise. I think where we are heading with the research is trying to understand how these genes function normally, how they are regulated, their expression is regulated, what their normal function is in cell growth, differentiation and division.

We have to develop new genetic ways for studying them because they are not really amenable to detailed study in higher animals in the way that, by classical genetics and bacterial genes can be studied.

And finally, we know that there are changes in some of the products that—a change in the products much like change in hemoglobin product results in sickle cell anemia, changes the structure of the protein. We have to know something about the structure and how that change translates into the structure, and if it causes a modification in the structure, it may be possible to target that particular gene that's product that's changed by knowing what the change in the structure is and deriving molecules that will interact specifically with that change region.

Thank you.

[The prepared statement of Dr. Vande Woude follows:]

STATUS AND IMPLICATIONS OF ONCOGENE RESEARCH HEARINGS

Statement by

GEORGE F. VANDE WOUDE, PH.D.
DIRECTOR, LBI-BASIC RESEARCH PROGRAM
NCI-FREDERICK CANCER RESEARCH FACILITY

Mr. Chairman and members of the Subcommittee, I appreciate the opportunity to appear before you today to discuss recent developments in science that are beginning to provide insights into the mechanisms of carcinogenesis. The purpose of this presentation is to describe to you our current concepts of oncogenes, how they are identified, and most importantly, how they are activated to produce tumors in animals. For a major portion of this century there has been considerable controversy over whether viruses are a cause of cancer or whether environmental insults to normal cell genes can initiate the cancer process. Only during the past four years have we learned that both viruses and genetic mutations can mediate neoplastic disease by similar mechanisms. Diverse basic research disciplines woven together by technological breakthroughs in molecular biology and genetic engineering have provided us with our first descriptions of the molecular elements responsible for triggering the events that lead to cancer. These recent achievements promise, with cautious optimism, important applications for clinical diagnostics in cancer. The terms retroviruses, oncogenes, and DNA transfection are part of a new vocabulary used to describe the molecular elements that have been implicated in the cancer process. To explain these achievements it is necessary to define some of the terminology we use.

All of the genetic information of an organism is encoded in a master molecule called DNA that is present in each living cell. The encoded genetic information in the DNA molecule can be thought of as musical pieces which are stored or recorded on a magnetic tape. Encoded in the DNA tape are discrete genetic functions called genes much as a medley of musical pieces are recorded on a tape as a series of discrete songs. In the cell, the DNA tape is condensed into bundles called chromosomes, but it is easier to visualize as a linear tape and if it were possible to measure it from end to end, it would be more than 1 meter long. Moreover, there are two copies of the DNA tape in every body cell (except sperm and egg cells), each encoding an estimated 50,000 or more genes. Thus, there are two copies of each gene, one from each parent. It is the differential expression of these genes that determines all genetic characteristics from animal speciation to cellular and tissue functions. To continue the model, like individual notes of a piece of music, genetic information is encoded in DNA by the precise ordering of four chemically distinct units called nucleotides. These nucleotides are linked together to form chains that can number several billion per DNA tape. The precise order of nucleotides, called the DNA sequence, is the absolute information in the genetic code. As a wrong note can mean the difference between music and noise, a single nucleotide change can modify or abolish the function of a gene.

It is now possible for us to determine the DNA or nucleotide sequence of any DNA segment and to thereby decipher some of the encoded information in each gene. In living cells the genetic information in the DNA tape is deciphered by infinitely more sophisticated metabolic processes. One process, called gene transcription, involves both the regulation of which genes are switched on in a cell (expressed) and the synthesis of a product from a single gene. The product is a copy or transcript of the gene's DNA sequence and is called RNA. The genes transcribed from the DNA tape in muscle cells differ from those transcribed in other tissues; for example, blood, brain, liver, etc. Each gene, therefore, consists of at least two parts - a switch portion which regulates its transcription and a portion which is transcribed or copied into RNA. An RNA transcript of a single gene in the DNA tape containing more than 50,000 genes is like playing a single music piece from a recorded medley. In any one cell, many but not all genes are played and some of the genes played in one cell type (muscle) are not played in another (liver, blood, etc.)

A second metabolic process involves the translation or decoding of the RNA gene transcript into functional cellular products or proteins. The red blood cell protein hemoglobin is an example. This protein is responsible for transporting oxygen to body cells and is the translation product of the hemoglobin gene RNA transcript. Hemoglobin is only produced in red blood cells and not in other organs, tissues, or cells. It is regulated to be transcribed or expressed only in the former cells. There are obviously many other examples, like the genes for nail and hair proteins, but the immunoglobulin genes responsible for producing antibody proteins are important for this presentation. Only certain cells in the blood express these genes, and it is now clear that one form of human lymphoma involves the switch portion of the immunoglobulin gene.

We have identified as few as 20 genes which have the ability to cause tumors in animals and because of this activity, we have termed them oncogenes. These genes are dispersed throughout the more than 50,000 estimated genes present in the DNA tape. We refer to them as proto-oncogenes in their normal state, but this name is misleading because these genes are not merely sitting in the DNA tape waiting to be activated as oncogenes. Their normal functions are apparently so absolutely essential for living processes, that nature has to accept the risk of their being activated as oncogenes. Because they have only recently been identified, we are quite ignorant of what their normal functions may be and how, as oncogenes, their normal functions are modified.

In addition to the above given reason of why we know they are important, we also know they are important because they have pedigrees or are conserved. A conserved gene can be compared to a conserved word. Even though over the centuries slight changes occur in spelling, an important word in the English language (such as father) derived from Greek (pater) is conserved in usage. Important genes present in man have their counterparts in other species; for example, the gene for hemoglobin can also be found in the red blood cells of fish. Its DNA sequence (spelling) may be slightly, different, but its function is conserved. Hemoglobin is an important gene and it is conserved throughout the vertebrate kingdom. Oncogenes are also conserved. Conservation of the gene sequence is a measure of importance but does not reveal anything about function. What normal functions the oncogenes perform remains an area of intense investigation. The conservation of oncogenes allows the study of their function in lower organisms whose genetics and physiology are well known. Indeed, many of the oncogenes that have been identified in association with human neoplastic disease were originally discovered in birds and rodents. While normal functions are not known, we can only speculate from their activation in tumor cells that they may be associated with the regulation of cell division.

From the study of retroviruses, we first learned of and were able to identify and isolate oncogenes. Infectious, cancer-causing retroviruses have been isolated from many avian and mammalian sources and can be divided into two classes based upon the interval of time between infection and the appearance of a tumor. One class produces disease in animals after long latent periods of more than 3 months. Generally, these viruses produce leukemias and lymphomas and are called leukemia or leukosis viruses. The second class, referred to as acute transforming retroviruses, can produce tumors in newborn animals in less than 2 weeks. These characteristics led early investigators to believe they had identified agents responsible for neoplastic disease. The difference between the latent periods of diseases caused by these two virus classes can be traced to differences in their genetic information. Each acute transforming retrovirus has acquired a gene from the host DNA tape and this gene as part of the virus is responsible for the rapid tumorigenesis. The early investigators were correct, they were close to identifying the agent responsible for tumors; but it was not a viral gene that was responsible, it was a cellular gene that had been placed under the transcription control of the virus. Of course, these genes are referred to as viral oncogenes and they were captured by these viruses during their infection and passage through cells. As part of the infection process, the virus inserts randomly into the DNA tape of the cell. In extremely rare events the insertion of the virus into the DNA next to an oncogene allows for the oncogene to be captured as part of the viral genetic information. The new virus, with the acquired oncogene, infects a new host cell and causes this cell to behave as a tumor cell. The rapid tumor formation is due to the direct infection of cells by a virally activated oncogene. We expect that these viruses can acquire genes other than oncogenes, but these are never detected because genes other than oncogenes do not confer a selective advantage for growth upon the virus nor the cell it infects. The acute transforming retroviruses are generated at extremely low frequencies in nature, but their discovery provided us with our first inventory of oncogenes.

We learned subsequently that the long latent period of leukemia viruses was due to low frequency insertion of the virus (which lacks an oncogene) adjacent to one of several cellular oncogenes present among the more than 50,000 genes in the DNA tape. With both the acute transforming retroviruses and the leukemia retroviruses, oncogene activation occurs because of the substitution of the viral switch (that regulates virus expression) for the normal regulatory switch of the oncogene. The normal proto-oncogene transcription switch is substituted with the virus switch. The former is regulated in a cell dependent fashion, the latter is not. This represented our first insight as to how oncogenes were activated.

We can now discuss how oncogenes have provided a common thread linking several distinct cancer research disciplines. One of the most dramatic fusions of knowledge has occurred between the fields of cytogenetics and molecular oncology. For more than 20 years cytogeneticists have been systematically characterizing chromosomal (condensed bundles of the DNA tape) aberrations in human malignancies by viewing in optical microscopes changes in chromosome structure. Their results are striking. In specific forms of human (and animal) malignancies, for example as in Burkitt's lymphoma, a characteristic (nonrandom) exchange (translocation) occurs between two specific pairs of chromosomes bundles. At the molecular level, this involves breaking the DNA tape in two places and rejoining it at the wrong positions. Imagine the excitement when it was discovered that the breakpoint and rejoining in the DNA tape was precisely in the locus of an oncogene. Even more extraordinary, a similar malignancy in mice also involves nonrandom chromosomal translocations and the breakpoint occurs at the very same conserved rodent oncogene. In both human and mouse translocations the oncogene locus in the DNA is brought into the vicinity of the switch for the immunoglobulin gene. Under normal circumstances, cells that are expressing immunoglobulin or antibody do not divide but are switched on to produce large quantities of antibody. As a result of the translocation, the switch for the immunoglobulin gene substitutes for the switch of the oncogene and, most likely, causes the cell which is normally quiescent to rapidly proliferate. The insertion of a retrovirus transcription switch adjacent to this same oncogene in birds causes a similar malignancy in this species. Thus, we have seen that a switch from a virus can activate an oncogene. Similarly, a chromosome abnormality which places the switch from a normal, cellular immunoglobulin gene adjacent to the same oncogene can lead to its activation.

Another example of a chromosome abnormality is called gene amplification. In this abnormality, instead of a single copy of the gene being present in the DNA, this region of the tape is amplified 20 to 50 times. This results in a higher than normal level of expression of the oncogene product which apparently causes unregulated cell proliferation.

Nonrandom chromosomal translocations as well as gene amplifications, are fine structure changes of chromosomal DNA that have been associated with a variety of mammalian and human tumors. We expect that these chromosomal alterations involve oncogene activation by models similar to that described above. Strong support for such models comes from the mapping of the individual oncogenes to specific human chromosomes or to specific positions in the DNA. This mapping allows association of known chromosomal changes in specific malignancies with oncogene positions in the DNA tape.

A number of other characteristic anomalies involving oncogenes have been identified in human leukemias. We expect that the breakpoints in the DNA tape will involve the switch of one locus that permits unregulated expression of the second locus, the latter being a cellular oncogene.

We have learned of other mechanisms for oncogene activation, primarily by use of a method called DNA transfection. This assay has been especially useful for identifying oncogenes in human tumor samples and is sufficiently sensitive so that if a single activated oncogene is present among the more than 50,000 genes in a DNA tape, it is possible to transfer this oncogene into nontransformed recipient mouse cells. Even if the oncogene is derived from human cells in the recipient mouse cells, the products of the gene responsible for tumorigenicity in the parental tissue can cause the recipient cell to become transformed. In this manner it has been possible to identify one class of activated oncogenes present in a large percentage of human tumors. With few exceptions it has been determined that these oncogenes are activated from proto-oncogenes by a change in a single nucleotide in the gene. Recall the analogy I made between notes in a musical piece and the nucleotide sequence of a gene. A one note change results in noise. One change in a nucleotide in the DNA sequence can change a particular oncogene family from proto-oncogenes to activated oncogenes. This situation is not without precedent. For example, sickle cell anemia is caused by a single nucleotide change in the hemoglobin gene. The difference between the oncogene activation and the sickle cell trait is that the latter is inherited. The change in a single nucleotide in the DNA sequence of the oncogene occurs in a single cell of an individual. The activation of an oncogene by a single nucleotide change can provide a growth advantage to cells harboring this gene in the same way as viruses with oncogenes can provide a selective advantage for cells to proliferate.

There are several other examples of oncogene activation which involve proteins called growth factors that promote cell growth. What we have learned is that several of the oncogenes correspond to the genes for these growth factors. Growth factors have been studied as a separate cancer research discipline and the discovery of their link with oncogenes has served to illustrate how some of the oncogene products can function.

The research endeavors in chemical carcinogenesis have provided excellent model systems for studying the tumorigenic activity of environmental pollutants. For example, the exposure of rodents to certain chemical carcinogens leads to the formation of specific tumors after a characteristic latent period. What we have recently learned from these animal systems is that chemical carcinogens activate the same cellular oncogenes that have been correlated with virus activation, gene amplification and, most importantly, with oncogene activation by a change in a single nucleotide of the DNA sequence, a long time suspected effect of certain carcinogens.

We have seen how information from distinct research disciplines has been woven together by techniques of molecular biology to give the first molecular descriptions of oncogenes. It is not surprising that these molecular changes involve specific genes that are highly conserved in evolution and have functions keyed to cell division and growth. We expect that the determination of their role in these processes will lead to an understanding of the mechanisms underlying normal and abnormal cellular functions. Specific probes to oncogenes and antibodies to their protein products could in the near future assist in diagnostic procedures to reveal the presence of molecular alterations present in specific tumors. For example, in the cases where oncogenes are activated by a single nucleotide change in the DNA sequence, antibody or nucleic acid probes directed against a specific region could permit detection. Rearrangements in genes, as in chromosomal breakpoints in translocations, could be detected by analysis of the arrangement of the genes in the DNA tape. Likewise, RNA transcripts from the oncogenes may have diagnostic utility especially in the cases where gene amplification has been associated with the neoplastic disease. These examples are only a hint of what should be available in the coming years. We may find that specific oncogenes are activated in each tumor type and that the characteristic morphology of a tumor cell can be correlated with the abnormal behavior of specific oncogenes.

There are numerous examples in which the knowledge of the entities responsible for disease led first to successful diagnostic reagents and procedures and subsequently to treatment and prevention. The most recent example was the identification of poliovirus as the agent responsible for poliomyelitis. Although cancer is infinitely more complex, we may be at a similar crossroad with oncogenes and cancer. Poliovirus is an extracellular genetic element responsible for poliomyelitis and the technology of that era portended its identification and isolation. The new techniques in molecular biology and genetic engineering likewise now permit us to identify and isolate the genetic elements associated with cancer. At the very least we will achieve success in applying this knowledge to diagnostic procedures.

Mr. **Gore**. Thank you very much.

We'll go now to Dr. Carl Sherr, chairman of the Division of Human Tumor Cell Biology at St. Jude's in Memphis.

Dr. **Sherr**. Thank you very much, Mr. Chairman. I had submitted, actually, what I thought would be a 5-minute testimony, and I had intended to read it, but I realize it's already entered in the record and so I thought I would just make some ad lib comments and perhaps cover some of the points that have already been raised by Drs. Temin and Vande Woude and elaborate on the function of oncogene products, which I was specifically asked to do.

Mr. **Gore**. Great.

Dr. **Sherr**. You raised a question about the terminology and I think it's interesting that oncogenes were originally identified as components of viruses which conferred on the viruses the properties of being able to alter the growth characteristics of cells grown in culture, and also produce cancer in animals, as Dr. Temin dramatically showed you.

Because of the historical definition of oncogenes in tumor formation, it was really a very important question to—to address where these genes came from and the realization that the genes came from normal cells suggested, then, to all of us, that these genes would probably play some important function in normal cells and logically, one would assume that that normal function was not to produce cancer.

And so the nomenclature was modified and the genes in normal cells are called proto-oncogenes to imply that changes in the genes can activate them and can result in their activity in cancer formation, but that these genes actually play a fundamental physiological role in normal cells.

We don't have a lot of information about what the role of these genes is, but it's been suggested by many investigators that these genes are involved in regulating the growth of normal cells, and as a result of alterations in the genes, they begin to inappropriately regulate the growth of cells in a way that leads to cancer, and therefore, the genes are probably important, either in initiation of tumors, or in properties of what we call "tumor cell progression," where tumors are altered in their genetic characteristics. For example, benign tumors frequently become malignant.

Now, Dr. Vande Woude has indicated that there are several mechanisms, genetic mechanisms, which are responsible for activation of these normal proto-oncogenes and unleashing their oncogenic potential, converting them into active oncogenic principles in cancer cells, or in tumor viruses, and in general, in cells, the mechanisms for activating these genes involve changes in the genes themselves, in the products that they encode, which are frequent consequences of mutation, dramatic rearrangements in the genes which involve actually movement of the genes or breakage in the genes as a result of translocation of chromosomes, for example, and also, more recently, we recognize that in some cases, the genes can be amplified and that instead of having one or two copies of each of these genes per cell, there may now be hundreds of copies of these genes so that even though their regulation may not be changed, the quantity of gene product produced by the amplified genes may increase.

On the basis of the fact that normal genes, then, are activated by—I should emphasize that a variety of environmental agents known to be etiologically associated with cancer are known to work through similar mechanisms and so we assume that environmental mutagens or carcinogens or radiation, which is known to break DNA, is going to ultimately find selective genetic targets, a subset of cellular proto-oncogenes, and by altering these genes lead to processes of tumor formation.

Now, what can we say about the products of these genes? Well, one of the logical assumptions would be that we would expect these products to mimic functions which normal cells ordinarily express. It's not to say that all normal cells may express these functions on the same timetable, and clearly, as Dr. Vande Woude has indicated, there have to be genetic processes which involve regulating the DNA and which impact on what makes one cell different from another. So that clearly, in any one cell, only a subset of the total genetic dowry is expressed at any one time.

On the other hand, at some time in the development of the organism, or in differentiation, one would assume that oncogenes are expressed and that the products of these genes then would reflect normal gene products that are expressed in the development and differentiation.

Now, there are about 20 proto-oncogenes and we are just now beginning to elucidate some of their functions. Perhaps the major class of proto-oncogenes has been found to encode unusual enzymes which have been referred to as tyrosine-specific protein kinases, and without discussing the actual function of these particular enzymes with you in detail, I simply would like to point out that there is a family of normal cellular proteins that have now been identified which express these same functions. There are at least three normal cellular proteins which are known to have associated tyrosine-specific protein kinases activity, and in each case, each of these proteins was found to be a receptor for an extra cellular growth factor, which is expressed at the cell surface of many different cell types.

And so, it was a reasonable assumption that perhaps proto-oncogenes could, in fact, be genes which code for protein receptors on the surfaces of cells, and by that mechanism, then, regulate the cellular response to extra cellular growth stimulatory compounds.

Within the last 4 months, we've realized that at least one of the known oncogenes, erbB, codes for, in fact, a protein which is now identified to be the receptor for epidermal growth factor, and so, in fact, this hypothesis has for the first time been reinforced by comparisons of normal receptor genes and proto-oncogene sequence previously.

Another class of proteins encoded by the so-called ras gene family may be similarly involved in regulating receptor functions at the cell surface. The proteins encoded by the ras genes have particular properties which suggest that they may be involved in receptor regulation, and very recently, Dr. Cooper's lab in Boston has reported the actual physical association of a ras gene product with one of the known cellular receptors, the transfer receptor.

In addition, if oncogenes can encode receptors, it might also be possible that they can directly encode hormones and within the last year, the sis gene has been demonstrated to code one of the polypeptide chains of platelet-derived growth factor. So there are now at least three examples in which the products of oncogenes have been found to be involved in receptor-mediated functions, either as hormones, receptors or receptor regulators. We presume that these gene products act at the cell's surface and, in fact, we do find those gene products there and it seems, then, that one level of regulating the growth of cells is probably endocrine and that aberrant control mechanisms, endocrine control mechanisms, may have some impact on tumor formation.

There are other families of oncogenes about which we know even less. The products of certain other genes, like the myc gene or the myb gene, are known to be expressed in the nucleus of cells and we really have not idea about their function.

In fact, it's only been within the last year or so that the application of recombinant DNA technology has allowed us to identify these products at all, and now we are in a position where we can actually express those gene products and in bacteria for the first time look at their detailed structure or generate antibodies to the gene products, but I emphasize with you that these are events that have come out of research really within the last 1 or 2 years. And certain of the results on these particular gene products are not even published at the present time.

We would assume, perhaps, that proteins expressed in the nucleus of cells might be involved in some other parameters of growth control like DNA replication, which is necessary for cell division or possibly that these products regulate the expression of other genes and that opens up the possibility that different oncogene products can collaborate with one another in inducing cellular transformation in tumors.

There's a recent report in the literature that, in fact, the product of the sis gene, which is, I've mentioned, a growth factor, actually induces expression of another oncogene product which is localized primarily in the nucleus, and so one can think about these gene products complementing one another in their biological activity and perhaps acting in concert in multistage carcinogenesis.

I think it's—it seems evident that we will develop, as a result of genetic engineering technology, new diagnostics for the study of these genes, although I emphasize that to date, there's been no direct clinical application of that technology that I'm aware of that impacts directly on the cancer question.

I think I'll stop.

[The prepared statement of Dr. Sherr follows:]

TESTIMONY

of

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Current evidence favors the view that tumor formation is mediated through the action of a discrete subset of cellular "proto-oncogenes" found in all cells. In normal tissues, these genes are proposed to play a physiologic role in governing cell proliferation and regulating the differentiation of independent cell types during development of the organism. In tumor cells, proto-oncogenes may be inappropriately expressed and genetically altered in such a way as to render their products more potent in promoting cell growth and malignancy. The mechanisms which unleash the latent tumorigenic potential of proto-oncogenes, converting them to active oncogenes, include gene amplification, chromosomal rearrangement, and mutation - genetic processes which are frequently the consequence of environmental agents known to induce tumor formation. Hence, multiple and diverse etiologic agents of cancer may conceivably act through defined genetic proto-oncogene targets. It seems evident that a more complete understanding of these genes and their encoded protein products will yield important new information about the processes of normal cell growth and differentiation and their pathologic counterparts in tumor formation and progression to malignancy.

Oncogenes were first identified in studies of RNA tumor viruses which have been known to produce cancers in animal model systems since the turn of the century. The ability of these viruses to produce tumors in their natural hosts and to dramatically alter the growth of cultured cells in vitro - a process termed "transformation" - is known to depend on oncogenes which were acquired by recombination between nontransforming viruses and proto-oncogene sequences present in the DNA of their hosts. Recent application of molecular biological techniques to the characterization of tumor viral genomes, and in particular of methodologies involving recombinant DNA, permitted viral oncogenes to be purified, thereby providing the first tools for identifying their proto-oncogene progenitors in the DNA of normal cells. These studies have been complemented by independent approaches which relied on DNA-mediated gene transfer to isolate active oncogenes from tumor cells and to transmit them to normal cells where they dominantly confer a malignant phenotype. The latter studies showed that oncogenes active in certain human tumors were identical to those acquired by known animal tumor viruses. Thus, the total number of proto-oncogenes in any one organism may be relatively few and their modes of action in regulating growth and differentiation would presumably apply to diverse cell types in different tissues. The terms "oncogene" and "proto-oncogenes" are therefore misnomers, stressing the historical identification of these genes in the context of tumor formation rather than their putative role as determinants of normal cell growth.

Approximately 20 different proto-oncogenes have been identified. These have been molecularly cloned, in some cases sequenced, and assigned to chromosomal locations within the human genome. About half of these genes encode unusual enzymes - tyrosine-specific protein kinases - which are membrane-associated and appear to function at the surface of cells. During the last few years, independent studies of membrane receptors which transduce extracellular hormone signals at the cell surface demonstrated that several classes of receptor proteins possessed tyrosine-specific protein kinase activities. The interaction of these receptors with specific growth promoting hormones (or "growth factors") elaborated by other cells triggers the receptor-associated enzyme activity which, in turn, is presumed to operate as an intracellular "second signal" in stimulating cell growth. Several laboratories, appreciating the functional similarities between these receptors and one major family of proto-oncogene products, considered the possibility that these two classes of proteins could be one and the same. Indeed, in the last few months, it was found that one of the known proto-oncogenes (c-erbB) is identical to the gene encoding the receptor for the growth stimulating hormone, epidermal growth factor (EGF). The interaction of specific extracellular hormone signals with the repertoire of receptors displayed on cells of different histogenetic lineages can regulate the growth of normal cells. It seems likely that alterations of receptor molecules themselves which render them hormonally-independent, or the inappropriate expression of receptors that are normally restricted to other cell types, could be important mechanisms of uncontrolled cell growth.

The exact mechanisms by which receptors transduce extracellular messages remain unclear. In certain systems, the responses of receptors can be amplified or attentuated by other classes of proteins which bind to the receptor molecules and modify their function. We suspect that another class of oncogenes - those designated c-ras - code for products which regulate receptor functions, since the nucleotide binding properties of these polypeptides, their location at the cell surface, and their recently demonstrated physical association with at least one class of receptor molecules is reminiscent of proteins known to modify receptor responses in several different systems. Proto-oncogenes can therefore code for products which govern the cellular response to exogenous growth promoting hormones.

If some proto-oncogenes code for hormone receptors or their regulators, it seems equally logical that other classes of proto-oncogenes could directly encode growth promoting hormones. Within the last year, the product of the c-*sis* oncogene was shown to be identical to one of the polypeptide chains of platelet-derived growth factor. In cells transformed by c-*sis*, the mechanism of tumor formation appears to involve the inappropriate expression of a growth promoting substance to which the cells themselves respond. Hence, at least three classes of oncogene products including receptors, their regulators, and hormones, influence cell growth through endocrine functions.

The products of several other proto-oncogenes appear to act in the nucleus of cells. At present, the role of these proteins remains obscure. It seems logical that they may act to regulate the expression of other genes or to control the replication of genetic material. Their site of action in the cell nucleus differentiates these products from hormones or receptors that act at the cell surface, and suggests that they could complement the functions of cytoplasmically expressed oncogene products. Indeed, it has been shown in model systems that the action of nuclear and cytoplasmic oncogene products acting in concert, can elicit cell transformation in cases where neither of the two genes acting alone produces a neoplastic conversion. These observations are consistent with data suggesting that tumor formation and the acquisition of malignant potential are multistep processes involving the products of multiple genetic loci.

We are now in the process of generating new tools to study the activity of proto-oncogenes in a variety of situations not necessarily restricted to tumorigenesis. The general availability of the molecularly cloned oncogenes has already led to several demonstrations that proto-oncogenes are activated in various forms of human cancer, supporting the view that altered forms of the gene products, or their elevated levels, might be detected in tumor cells. The ability to use recombinant DNA techniques to engineer the production of significant quantities of oncogene products in simple unicellular organisms like bacteria or yeast affords the first opportunity to purify and biochemically analyze these proteins. Antibodies which detect the products of oncogenes have come into general laboratory use in just the last few years, and may conceivably prove to be of diagnostic utility in the near future.

Although work in this area appears to be proceeding at an explosive pace - at least to those of us actually working in the field - one senses that we are just beginning to unravel the functions of these genes. None of the work to date has been of direct clinical application, and it is quite possible that the ultimate payoffs may come from unexpected directions. for example, studies of the role of proto-oncogene products as cell surface receptors could eventually prove as important to an understanding of diabetes or atherosclerosis as of cancer. the excitement among us comes from the intensifying general belief that work on these fundamental problems in tumor biology will, in the near future, yield insights of major clinical significance.

Respectfully submitted:

Charles J Sh

Charles J. Sherr, M.D., Ph.D.

Mr. GORE. Thank you. That was an excellent statement, very helpful.

We have one other witness to round out this panel and then we'll go to questions. Dr. Stuart Aaronson is Chief of the Laboratory of Cellular and Molecular Biology at NIH and NCI and, Dr. Aaronson, your prepared statement's in the record and if you could give us the meat of it, we'd appreciate it.

Dr. AARONSON. I very much appreciate the opportunity to appear here today and I think a number of these investigators have highlighted the gist of what's going on in this area of research. What I'll try to do in this—in the brief time, is talk about two very important areas and possibly a little bit about how we might apply knowledge that's been gained to either diagnosis or treatment.

Could I have the first slide.

[Slide 1.]

Dr. AARONSON. The points that have been raised earlier indicate that we're dealing with a small set of genes we call proto-oncogenes and I think that—to emphasize a point that may not have been brought out is that long before we knew anything about function, we knew that genes related to the genes that these viruses had captured were really present, not only in mice and rats and chickens and even human cells, but also present in much lower forms of life, including even flies and yeast. And when you have a gene that's present in all forms of life, you know that it has to be very important for some essential life function. That's what we mean when we say "conserved" in evolution. And that's what each of these proto-oncogenes really is, a highly conserved cellular gene.

Mr. GORE. In Dr. Vande Woude's prepared statement, he had an analogy which was helpful to my understanding by comparing it to the conservation of important words and various languages. The word "pater" from Greek and father in English. The versions of it may be different, but they are present in whole families of languages and similarly, these proto-oncogenes are slightly varied in the different vertebrate species, but they are so similar that they're readily recognizable.

Dr. AARONSON. Right.

Mr. GORE. And you infer from that that they—that they have to play a critical evolutionary role.

Dr. AARONSON. In the next slide——

[Slide 2.]

Dr. AARONSON [continuing]. To give you the background with this, my rapidly done medical illustration yesterday, this is to depict three normal cells. On the surfaces of these cells, you see specific receptors and floating in, you see either a hormone or a growth factor which, by a lock and key mechanism, the right hormone with the right receptor causes, through a sequence of events that are really not yet understood, the triggering of the normal cell's growth.

Now, there are a number of hormones or growth factors and there are certainly a number of receptors that are specific for each. But you can see that it would be very bad for a cell to make a growth factor, for example, for which it had its own receptor. If so, you might envision a situation in which essentially the cell became turned on by its own product. So that, in general, hormones are made by one cell and another cell type responds to that particular hormone.

Next slide.

[Slide 3.]

Dr. AARONSON. Now, I just wanted to show a DNA sequence just because probably we haven't had one of those shown in one of these hearing rooms, but I don't want you to know anything more than to know that what—what this represents is really the results of basic research from three different disciplines. In our laboratory, the sequence of a transforming gene of a virus predicted an amino acid sequence. In a completely different field, a field in which workers were trying to study the structure of a growth factor, they sequenced the protein. Another scientist, in a completely different place, who's interested in how proteins evolve, how they compare with one another, and has a big computer bank to plug in all known sequences, put the published sequences of these two different gene products into his computer bank and what you really see here in the shaded area is what was the first match between the product of a known gene, a known cellular gene, and one of our oncogenes.

This was, in fact, the match that led us to understand that the cis oncogene from a virus that we were working on, was matched with one of the proteins that is part of a growth factor that we call platelet-derived growth factor.

Now, next slide.

[Slide 4.]

Dr. AARONSON. Now, in this cartoon, what we really know about platelet-derived growth factor is it is, in fact, found and stored within the platelet, which is a blood cell, and what is thought to occur is that when a wound forms, platelets are very fragile and disrupt and they release this growth factor, which has as its specific target, connective tissue cells that are very important in the process of wound healing.

And so, what you see in the top is the limited proliferation of normal connective tissue cells responding to this particular growth factor at the site of a wound.

Now, in using your analogy, which I find quite nice, if we were to hot-wire the gene for that growth factor in a cell that would be responsive to it, we have evidence that this, in fact, occurs in brain tumors and in certain kinds of sarcomas, we would stimulate a cycle of continuous cell growth which we believe to be one step in the neoplastic process.

Now, what can we do about it? Well, it's a problem. These are the genes within us, but if, in fact, there is a growth factor produced that stimulates that cell to proliferate, it is at least conceivable to think about the possibility, admittedly speculative, of designing molecules that would still fit the lock, but would, instead of triggering that receptor, simply bind it and block the action of the bad protein. So, in this case, we have a situation, admittedly, as we said, speculative, in which the turning on of a normal gene product, which would stimulate in a good way a very important cell process, in the wrong cell type, may be a step in the carcinogenic process.

Next slide.

[Slide 5.]

Mr. **Gore**. To torture the analogy, you hope to be able to take the distributor cap off so it can't be hot-wired. [Laughter.]

Dr. **Aaronson**. We're going to have to write some of these things down.

Now, in the case of a certain kind as Dr. Vande Woude, Dr. Temin have mentioned, in human tumors, you see evidence that these proto-oncogenes can be activated by a variety of mechanisms and George has talked about chromosome translocation and gene amplification. And what I'll mention to you is studies that have shown us that even the most subtle of all genetic changes, the change of one structural part—my goodness—of the DNA sequence of a gene, can lead its protein to acquire transforming properties.

Next slide.

[Slide 6.]

Dr. **Aaronson**. This is seen again in a cartoon. Literally, if we take a human tumor and extract its genetic material, as shown on the left top by a method that we call transfection, which simply means taking that DNA and dumping it onto a susceptible assay cell, a cell which, in the bottom, when that DNA is added, 20 percent of human cancers will induce the formation in those normal cells of altered cells that we call transformed foci and—a picture of which Dr. Temin essentially showed you a little bit earlier. Those cells that are altered can be put into a mouse and cause a tumor, and in those cells, human oncogenes can be found, isolated, cloned and characterized.

The fact that 20-or-more percent of human cancers of all kinds, sarcomas, carcinomas, hematopoietic tumors, have shown us that they contain an oncogene of exactly the same type, an oncogene which, parenthetically, is related to one of the genes that first came to our attention because it was captured by a retrovirus. I think it tells us, again, something that the others have emphasized as well, that we're dealing not with a multitude of mechanisms of carciongenesis, but with what are apparently a relatively few number of common pathways.

To show you, in the next slide——

[Slide 7.]

Dr. **Aaronson** [continuing]. This is, again, a cartoon which shows us a normal proto-oncogene, which we call ras, 189 amino acids, the building blocks of the protein that it codes, makes a particular protein shown on the left. We now know that in all of those cancers in which this gene is activated as an oncogene, a simple change in one place, either at the 12th or the 61st position of its coding sequence, leads that gene product to acquire transforming properties.

And what you can see here in this rapidly made illustration yesterday is that the protein coded by either of the 12th or the 61st position mutated ras proto-oncogene, which is now an oncogene, is different, at least somewhat different, from that of its normal counterpart. And if we're lucky enough to develop reagents which will specifically detect the altered forms of that normal protein, we believe that it may be useful in the more early, more rapid diagnosis of cancer.

Next slide.

[Slide 8.]

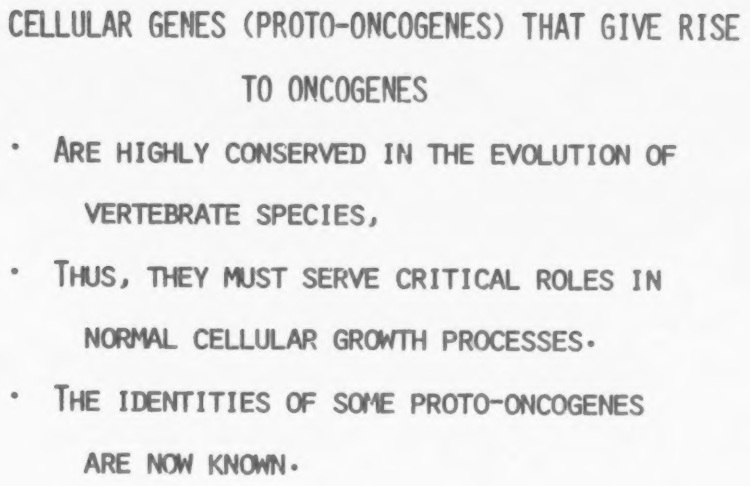
Dr. **Aaronson**. So in summary, what I think we've all been trying to explain is that the normal cell is literally composed of dozens of thousands of working parts, coded for by all of these gene sequences that are present on that big tape. To try to understand all of the normal working parts and how they interact and let alone then find out how they then become bad and lead to a cancer cell is a difficult problem. You know, it was a monumental task. At the time we were trying to go to the Moon, we were also trying to develop handles on this kind of a problem.

We have found over the last several years, through advances in basic research, many of those advances brought by areas, for example, recombinant DNA technology which came from workers interested in how bacteria work. We now know that at least a very few genes within the cell commonly can go bad in a variety of ways.

Some of the mechanisms, as we've said, are precisely known, and what that may be helping us to understand, at least, is that the common pathways leading to cancer may involve a relatively few genes. If we can understand them, if we can develop strategies from that understanding, we hope we'll be in a better position, both for diagnosis and treatment of cancer.

Thanks.

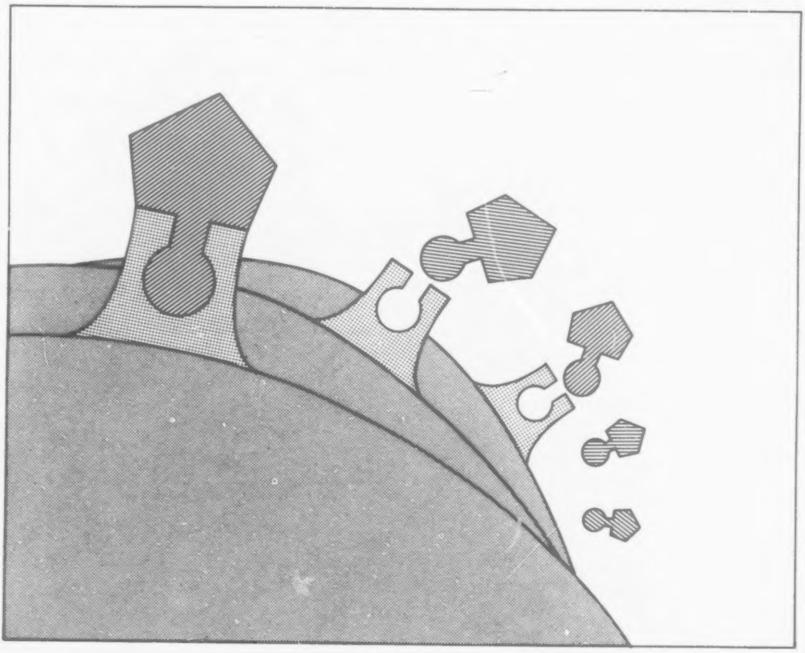
[Slides 1 thru 8 of Dr. Aaronson's oral statement, plus his prepared statement follows:]



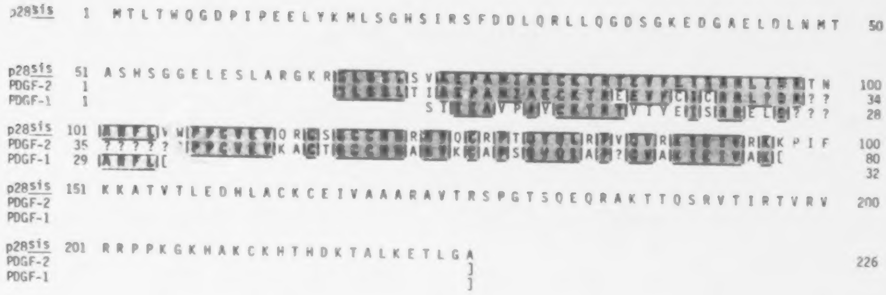
CELLULAR GENES (PROTO-ONCOGENES) THAT GIVE RISE TO ONCOGENES

- ARE HIGHLY CONSERVED IN THE EVOLUTION OF VERTEBRATE SPECIES,
- THUS, THEY MUST SERVE CRITICAL ROLES IN NORMAL CELLULAR GROWTH PROCESSES.
- THE IDENTITIES OF SOME PROTO-ONCOGENES ARE NOW KNOWN.

SLIDE 1



SLIDE 2



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p28sis   1  M T L T W Q G D P I P E E L Y K M L S G H S I R S F D D L Q R L L Q G D S G K E D G A E L D L N M T     50

p28sis  51  A S H S G G E L E S L A R G K R [illegible] S V [illegible] T N     100
PDGF-2   1                                 [illegible] T I [illegible] ? ?     34
PDGF-1   1                                      S T [illegible] ? ? ?     28

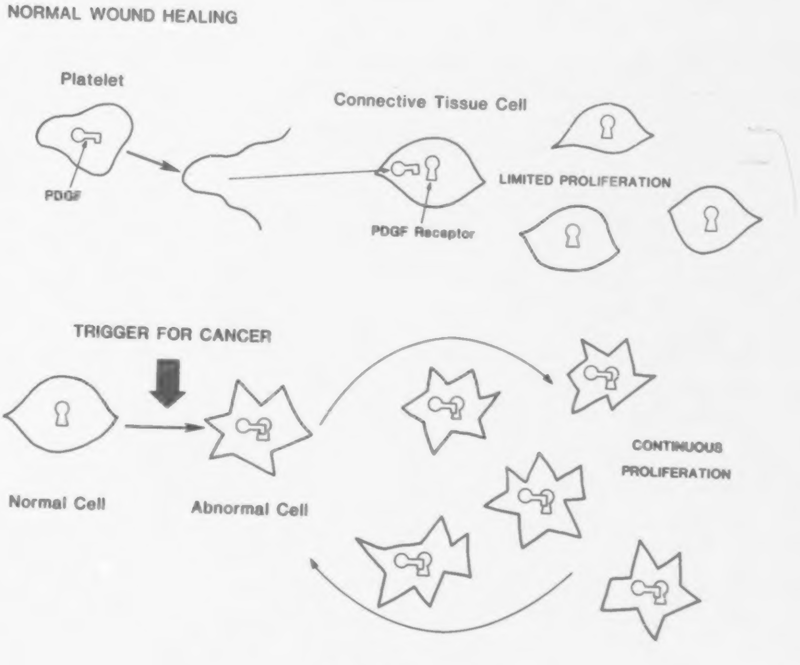
p28sis 101  [illegible] V W [illegible] Q R [illegible] R K K P I F     100
PDGF-2  35  ? ? ? ? ? ? [illegible] K A [illegible]     80
PDGF-1  29  [illegible] [     32

p28sis 151  K K A T V T L E D H L A C K C E I V A A A R A V T R S P G T S Q E Q R A K T T Q S R V T I R T V R V     200
PDGF-2
PDGF-1

p28sis 201  R R P P K G K H A K C K H T H D K T A L K E T L G A     226
PDGF-2                                                    ]
PDGF-1                                                    ]
```

A, alanine; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

SLIDE 3


NORMAL WOUND HEALING
Platelet
PDGF
Connective Tissue Cell
PDGF Receptor
LIMITED PROLIFERATION
TRIGGER FOR CANCER
Normal Cell
Abnormal Cell
CONTINUOUS
PROLIFERATION

SLIDE 4

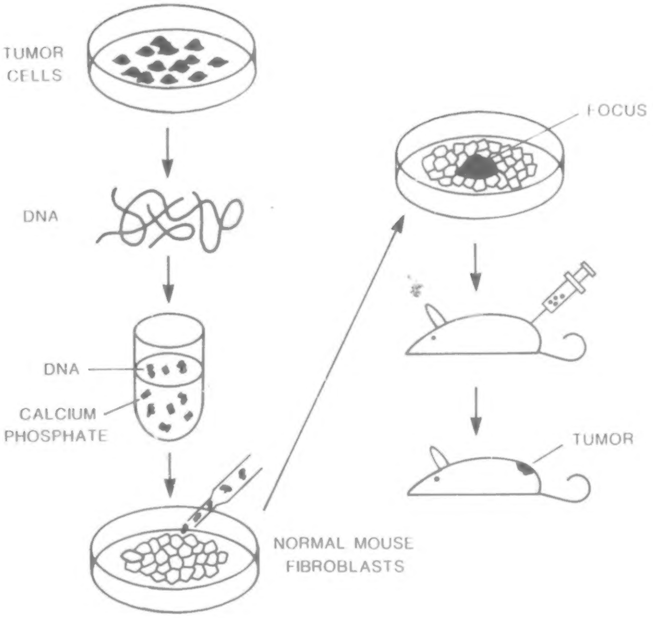
ONCOGENES RELATED TO RETROVIRAL onc GENES

CAN BE ACTIVATED IN HUMAN TUMORS BY:

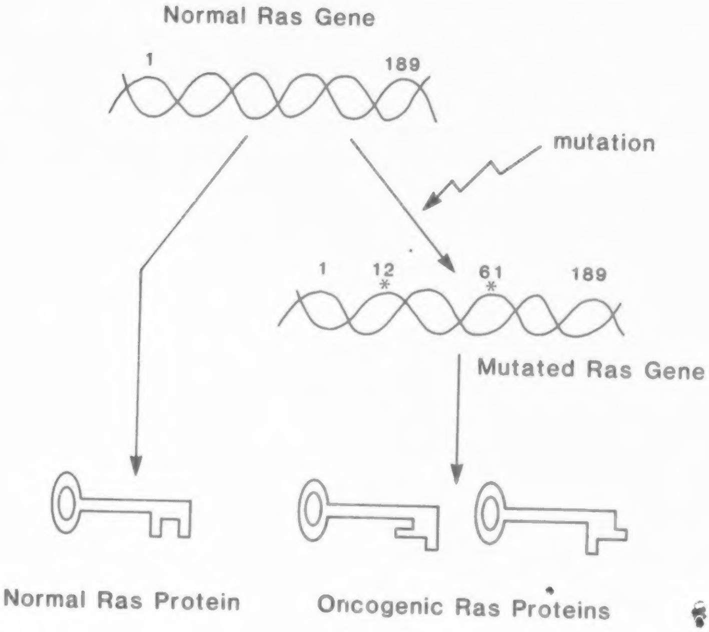
Mechanisms

- Chromosomal translocation
- Point mutation
- Gene amplification

SLIDE 5

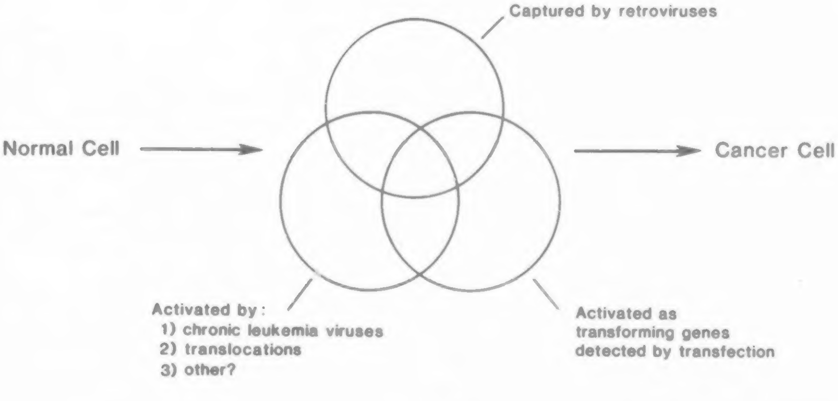

TUMOR CELLS
DNA
DNA
CALCIUM PHOSPHATE
NORMAL MOUSE FIBROBLASTS
FOCUS
TUMOR

SLIDE 6


Normal Ras Gene
1
189
mutation
1
12
61
189
Mutated Ras Gene
Normal Ras Protein
Oncogenic Ras Proteins

SLIDE 7

Cellular
ONC Genes


Captured by retroviruses
Normal Cell
Cancer Cell
Activated by:
1) chronic leukemia viruses
2) translocations
3) other?
Activated as
transforming genes
detected by transfection

SLIDE 8

STATEMENT

BY

STUART A. AARONSON, M.D.

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NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to appear before you today to discuss advances in the area of oncogene research. This is perhaps one of the most important and certainly one of the most exciting areas of investigation in in cancer research. My presentation will address the origin of oncogenes, and the studies and findings linking this small set of cellular genes to the neoplastic process affecting human cells. I will also try to explain why this area of research has given scientists optimism for the development of new approaches to diagnosis and treatment of human cancer.

Efforts to elucidate the genetic alterations that lead normal cells to become cancer cells have been aided immeasurably by the investigation of acute transforming retroviruses utilizing technological advances in the area of molecular biology. Acute transforming viruses have substituted viral genes required for replication with discrete segments of host cellular information. When incorporated within the viral genome, these transduced sequences, designated onc genes, acquire transforming properties.

In the past few years, evidence has emerged that some of the very same normal cellular genes which have given rise to retroviral onc genes can be activated as transforming genes by mechanisms completely independent of retrovirus involvement. There is also evidence that has linked some of their cell-derived transforming genes to cellular genes activated to become oncogenes of human cancer cells.

Acute transforming retroviruses can cause a variety of malignancies, including sarcomas, carcinomas and hematopoietic tumors. In tissue culture, these agents rapidly induce growth alterations in susceptible target cells. Such transformants, after propagation in culture, produce tumors in animals, whereas uninfected cells in parallel cultures do not. Thus, the induction of transformed foci by the virus directly reflects its tumor-inducing capability in vivo.

Advances in recombinant DNA technology have made it possible to clone the proviral forms of these RNA viruses. The retrovirus genome contains long terminal repeat sequences, designated LTRs, which possess signals for the initiation, enhancement, and termination of transcription. However, the prototype acute transforming virus has deleted substantial information necessary for replication functions and has substituted, instead, a discrete new segment of information. Specific alteration or deletion of the substitution sequence causes the virus to lose its ability to transform cells or cause tumors. Analogous findings with a number of acute transforming viruses have led to assignment of the viral transforming function(s) to the acquired onc sequence.

If a retroviral onc sequence is used as a DNA probe to analyze normal cellular DNAs, the probe detects homologous sequences in DNAs of a wide range of vertebrate species. These findings, in addition to the fact that onc sequences are generally represented at single copy numbers, imply that viral onc genes have arisen from normal cellular genes. Evidence that these genes, designated proto-oncogenes, are also conserved in evolution further implies that they serve very important functions in normal cellular processes.

If any of the thousands of genes that exist in our cells could acquire neoplastic properties when captured by one of these viruses, then we would never expect to observe the same sequence incorporated by more than one of the known two dozen or so acute transforming retrovirus isolates. In fact, several virus isolates from the same or even different species have captured the very same onc sequence. These findings have indicated that the number of cellular genes that can acquire transforming properties when incorporated within the retrovirus genome must be rather limited.

Investigations aimed at elucidating the functions of the cellular genes that give rise to onc genes have in some cases led to detection of their transforming proteins. With one group of onc genes, the prototype of which is the src gene of Rous sarcoma virus, it has been possible to assign an enzymatic activity to the gene product. These genes code for protein kinases having specificity for tyrosine residues. However, identification of the function of proto-oncogenes from which oncogenes have arisen has, until recently, not been effected.

Studies with simian sarcoma virus (SSV), the only acute transforming retrovirus of primate origin, have been particularly informative. Having developed an appropriate biologic system for SSV characterization, the SSV genome was cloned, its structure dissected, and its cell-derived onc gene, v-sis identified. Subsequently the nucleotide sequence of the complete SSV genome was determined, and a protein (p28sis) established as the product of the SSV transforming gene. It has been found that the v-sis oncogene is very closely related to a gene coding for platelet-derived growth factor (PDGF).

Human PDGF is a potent mitogen for connective tissue cells, and is biologically important because it is thought to be involved in wound healing. Amino acid sequencing studies have shown that 87% of the amino acid sequence determined for PDGF matched that predicted for p28sis. Thus p28sis and PDGF appear to be derived from the same cellular gene.

The high degree of relatedness between the transforming gene product of a primate sarcoma virus and a potent growth factor for human fibroblasts, smooth muscle cells, and glial cells, suggest that the mechanism by which this onc gene transforms cells may involve the constitutive expression of a gene encoding a normal growth factor.

Recent studies have provided an additional link between growth factors and oncogenes. Purification of the cellular receptor for epidermal growth factor (EGF) has led to the elucidation of a portion of its amino acid sequence. A computer search has revealed a very close similarity between the EGF receptor and the product of the erb-B onc gene. Thus, transformation by another acute transforming retrovirus may also involve pathways through which growth factors exert their proliferative effects.

Since genes related to retroviral onc genes are present in human DNA, it became possible to assess the role of proto-oncogenes in the etiology of human cancers. One approach has involved the chromosomal mapping of human proto-oncogenes, and this approach has indicated that proto-oncogenes are widely distributed throughout the human genome. Thus, *sis* has been assigned to chromosome 22, the oncogenes *mos* and *myc* to chromosome 8, and *myb* to chromosome 6. Members of the *ras* oncogene family are found on chromosomes 1 (N-*ras*), 6 (K-*ras*), 11 (H-*ras*-1), and 12 (K-*ras*-2). Additional proto-oncogenes have been localized to chromosomes 3 (*raf-1*), 4 (*raf*-2), 5 (*fms*), 15 (*fes*), 22 (*abl*), and X (H-*ras*-2).

That specific chromosomal rearrangements were known to occur in certain human tumors raised the possibility that *onc* genes might be activated by chromosomal translocations. Indeed, chromosomes harboring *onc*-related genes are involved in several such diseases. For example, it has been possible to show that in the case of Burkitts lymphoma, the c-*myc* locus is translocated from chromosome 8 to chromosome 14. Moreover, evidence has been obtained indicating that these tumor cells express increased levels of the *myc* RNA, implying that the rearrangement of *myc* causes the gene to be subject to a new regulatory influence. The high degree of specificity of *myc* rearrangement in Burkitt's lymphoma supports the concept that it plays a role in the etiology of this tumor.

Human chronic myelogenous leukemia demonstrates a different translocation, termed the Philadelphia chromosome, involving chromosomes 9 and 22. Recent studies suggest that a translocation of the proto-oncogene related to the *onc* gene, *abl*, from chromosome 9 to chromosome 22 leads to its rearrangement as well as to the expression of an aberrant *abl* transcript. Thus, this approach appears to hold great promise in identifying proto-oncogenes which are targets for genetic alterations associated with chromosomal aberrations.

Chronic leukemia viruses lack a specific _onc_ gene sequence. Recent studies have provided evidence that their mechanisms of malignant transformation involve the activation of cellular proto-oncogenes by the nearby integration of regulatory sequences located within the viral LTR. Recent studies have also provided evidence for oncogene activation in naturally occurring tumors by transposition of endogenous cellular DNA sequences containing regulatory signals.

Another approach toward detecting transforming genes was initiated a few years ago. By the use of a sensitive technique for incorporating exogenous DNA into cells, termed DNA transfection, investigators asked whether DNAs of animal or human tumor cells possessed the capacity to directly confer the neoplastic phenotype to a susceptible cell. such results might indicate the presence of a "transforming gene" in the tumor. In fact, some human tumor DNAs were shown to induce transformed foci in the continuous NIH/3T3 mouse cell line, which was highly susceptible to the uptake and stable incorporation of exogenous DNA.

In one series of solid tumors examined for transforming DNA sequences oncogenes were demonstrated in about 15% of the fresh tumors tested, including two colon carcinomas, carcinomas of the lung and pancreas, and an embryonal rhabdomyosarcoma. Transforming genes were also detected in cell lines established from carcinomas of the colon, lung, gall bladder, urinary bladder, as well as from a fibrosarcoma.

In a series of 22 established human hematopoietic tumor cell lines or primary tumors, seven were positive in the DNA transfection assay. The frequency at which transforming genes were detected in hematopoietic tumor cell lines and primary malignancies was similar to that observed with solid tumors.

Many human oncogenes that have been detected by transfection analysis are related to a small group of retroviral oncogenes, designated ras. Although these oncogenes arise from different cellular genes, sequence comparison and immunologic analysis of their protein products revealed their high degree of homology and, hence, evolutionary relatedness.

It is striking that a very high fraction of the transforming DNA sequences associated with solid and hematopoeitic tumors analyzed to date are related to members of the ras gene family. Not only can a variety of tumor types contain the same activated ras oncogene, but the same tumor type can contain different activated ras oncogenes. These findings strongly imply that ras oncogenes detected in the NIH/3T3 transfection assay are not specific to a given stage of cell differentiation or tissue type.

Retroviruses that contain ras-related onc genes are known to possess a wide spectrum of target cells for transformation in vivo and in vitro. In addition to inducing sarcomas and transforming fibroblasts, these viruses are capable of inducing tumors of immature lymphoid cells. They also can stimulate the proliferation of erythroblasts and can even induce alterations in the growth and differentiation of epithelial cells. Thus, the wide array of tissue types that can be induced to proliferate abnormally by these onc genes may help to explain the high frequency of detection of their activated human homologues in diverse human tumors.

The availability of molecular clones of the normal and activated alleles of human ras proto-oncogenes now makes it possible to determine the molecular mechanisms responsible for the malignant conversion of these genes. The genetic lesions responsible for activation of a number of ras oncogenes have been localized to single base changes in their p21 coding sequences. In the T24/EJ bladder carcinoma oncogene, a transversion of a guanine to a thymine causes a valine residue to be incorporated instead of a glycine into the 12th position of the predicted p21 primary structure. Another oncogene designated Hs242, from a human lung carcinoma, has also been identified as an activated H-ras (human) proto-oncogene, making it possible to compare the mechanisms by which the same human proto-oncogene has been independently activated in human tumor-derived cells.

The position of the genetic lesion in Hs242 leading to its malignant activation has been identified and it was found that the Hs242 oncogene and H-ras (human) differed by a single base. This base change (adenine to thymine) resulted in the replacement of glutamine by leucine in this codon. Thus, a single amino acid substitution seems sufficient to confer transforming properties on the product of the Hs242 oncogene. These results also established that the site of activation in the Hs242 oncogene was totally different from that of the T24/EJ oncogene.

Subsequent studies have assessed the generality of point mutations as the basis for acquisition of malignant properties by ras proto-oncogenes by molecularly cloning and analyzing other activated ras oncogenes. Thus far it appears that mutations at positions 12 or 61 may be the genetic lesions most commonly responsible for activation of ras oncogenes under natural conditions in human tumor cells.

The number of genetic alterations required for neoplastic transformation remains to be elucidated. In cell culture systems, transfection of primary rat embryo fibroblasts with two oncogenes, ras and myc or ras and an early gene of the adenovirus genome EA, has been reported to be sufficient to induce the malignant phenotype, whereas either transforming gene alone is unable to do so. Such findings suggest that the number of discrete steps in the neoplastic pathway may be relatively few, and that there may be complementing groups of oncogenes.

There is a great likelihood that not all of the proto-oncogenes capable of being activated as oncogenes have been discovered. Moreover, genetically predisposing states certainly exist but likely involve recessive alterations whose effects are more subtle than that of the germ line transmission of an activated oncogene. Finally, the few genes which have already been identified as targets of the neoplastic process are highly conserved and in their unaltered state almost certainly are involved in essential growth proccesses. Thus, any attempt to intervene in such normal functions is likely to be difficult. Nevertheless, the evidence obtained so far strongly argues that the problem of deciphering the neoplastic process is becoming less complex and, thus, more approachable. If so, it is likely that continued investigation of this small group of proto-oncogenes will provide important insights into strategies that may eventually be useful in the diagnosis, treatment, and it is hoped even prevention of human cancer.

Implications

Recent investigations have identified a small set of cellular genes which appear to be frequent targets for genetic alterations leading to human cancer. These findings offer an unparalleled opportunity to determine the important pathways involved in the neoplastic process. Future efforts will be directed at determining the mechanism(s) responsible for the activation of oncogenes in human cancers. A major focus will be on identifying the cellular targets of oncogenes which can be activated by chemical mutagens and viruses, thus unifying cancer causation and relating these to environmental factors as well. To this end, additional proto-oncogenes and their functions will be identified, and normal and abnormal oncogene products will be compared to determine at which stage abnormalities occur. Using this approach it may be possible to interrupt this process by biochemical and/or genetic means. Since it is now possible by recombinant technology to make large quantities of cloned oncogene products, attempts will be made to identify specific purified oncogene products and to determine their structure and active site(s). With such knowledge, it may be possible to design specific inhibitors to interfere with their mode of action. Specific probes will be developed that will enable the characterization of specific tumors yielding additional and sensitive molecular-diagnostic tools for the pathologist. The diagnostic use of oncogene probes may also make it possible to relate various tumor-related events and oncogene protein expression to specific tumor types, resulting in a tumor "map." Complete maps may some day be developed relating unique tumor parameters to specific molecular events that can be evaluated diagnostically using oncogene markers.

Mr. GORE. Thank you very much.

I'd like to welcome some visitors from the National Assembly in Taiwan under the auspices of the Congressional Foundation. We're delighted to have you here.

Just a brief word of explanation. We have generally two types of hearings in the Congress. One is a legislative hearing, which leads directly to consideration of a bill or resolution; and then we have investigative hearings or oversight hearings, which are designed to explore discrete topics and find out what the Congress ought to consider doing in the future, or what the executive branch ought to do to seize an opportunity or to solve a problem or what not. And today, we're looking at the body of new discoveries related to oncogenes, which are cumulatively very exciting and constitute, in my view, a breakthrough. The word "breakthrough" is something scientists shy away from, but it's a very important set of discoveries about the genesis of cancer.

I'd like to recognize my colleague, Congresswoman Schneider, for questions.

Mrs. SCHNEIDER. Thank you. Let me apologize to the panel for my tardiness, but I regret that I have three hearings going on simultaneously and it's difficult to be in three places at once. But needless to say, I did have the opportunity to review some of the testimony that you've submitted in advance, because this area is of great interest to me, not only because I've personally had cancer and have had it in the family, but also Rhode Island, my—the State which I represent, is one of the highest in terms of cancer death rates. And so I have a lot of interest.

Let me begin with my more technical question and then phase into the pedestrian questions that I'm often asked and translate into when, how soon and how much. But—and anyone of you may answer this—are oncogenes only found in viruses? Is that the only place that they're found?

Dr. **Temin**. This question is a matter of definition. The technical definition, the strict definition of an oncogene would only be in viruses, because only in viruses can we apply the very strictest kind of definition. The more accurate definition is that oncogenes have now not only been found in viruses, but also in many cancer cells and furthermore, genes related to oncogenes are found in all normal cells, including humans, including fruit flies, including yeast.

So that genes related to oncogenes are distributed essentially in all animal cells and the oncogenes are present both in the viruses and in cancer cells.

Mrs. **Schneider**. So is it pretty well understood, then, that we can identify the oncogenes, where they are and their makeup, but the real question that remains is the process, the translation of them from a healthy cell to a diseased cell?

Dr. **Temin**. We understand at the genetic level the nature of the change from the normal proto-oncogene to the oncogene. This involves base pair mutation, antigene duplication or amplification, translocation, insertion. We understand these genetic processes. They fall under the general heading of mutation.

Mrs. **Schneider**. OK.

Dr. **Temin**. What we don't understand is, given now that we have these altered normal genes, exactly how does the new proteins that are made, or the more protein that's made, exactly how does that make the cell a cancer cell?

Dr. Aaronson has indicated one suggestion is that it makes more of a factor which causes the cell to divide more. This may be part of it, but this is only one thing. Going from an altered gene to what we call the final phenotype, filling in that is the real question, or in medical terms, the real question is preventing going from the altered gene to the cancer phenotype.

Mrs. **Schneider**. Uh-huh.

Dr. Aaronson, I wonder if you could explain a little bit about the tumor map that you mentioned in your testimony and how it could be used diagnostically.

Dr. **Aaronson**. Tumor map?

Mrs. **Schneider**. Well, the——

Dr. **Aaronson**. Maybe could that have been——

Mrs. **Schneider**. The common pathways——

Dr. **Aaronson**. Oh, common pathways——

Mrs. **Schneider** [continuing]. That you're referring to.

Dr. **Aaronson**. Common pathways, I think, were—again, what we're trying to convey is the concept that from—from so many thousand genes, only a very few are consistently coming up as oncogenes in a variety of different situations, captured by a virus, amplified in a tumor cell, activated as a transforming gene by this method of DNA transfection that I showed you, that it must be telling us that we're dealing with common pathways.

Our job, as Dr. Temin has just said, is to fill in all of the gaps. It's not as simple as a one change leading to a cancer cell; there's probably several steps in the process and the biggest problem is that, unlike a virus that comes from outside and goes in, in which a vaccine approach is very realistic and has been proven, these are essentially the seeds within us. We can't live without these genes——

Mrs. **Schneider**. Uh-huh.

Dr. **Aaronson** [continuing]. They're important. We know that—that spontaneous changes do occur. How do we deal with the problem of preventing those bad things from happening or blocking the bad results of those changes? Those are tough problems. Nobody is—nobody is promising a rose garden.

Mrs. **Schneider**. Well, that's my next question. What should our expectations be and what would be realistic for us to think of in terms of time lines? Let's start there.

Dr. **Aaronson**. I think I hope we would all agree that there is going to be a fairly large-scale emphasis at this point on at least developing more rapid, more sensitive, specific diagnostic approaches toward cancer. If you can detect the problem earlier, you're going to have a much better chance of stopping it from being the serious problem that it can become.

So I think that within the realm of cancer diagnosis, I think that's probably where we'll see our first—you know, our first fallout of this research. The length of time that it will take is again going to be—I would defer to my senior colleague over here on the left.

Dr. **Temin**. The answer is if we knew how to do things, then it's very quick. Unfortunately, what we're requiring in terms of interrupting this sequence is something we don't know yet, and because we don't know yet, prediction tells us about the person making—making the prediction. If we're lucky, it could be that next year someone will come up with something which will work. If we're unlucky, it could take a much larger time and I don't believe it's predictable because it depends on something we don't know.

What we do know is a lot of people with the support of—of the NIH and the American Cancer Society, are working on these problems and we're hopeful that it will be sooner rather than later, but at the present time, there's no realistic way to tell you how soon that's going to be.

Mrs. **Schneider**. Thank you.

My final question is relating to the expense involved and to what degree is our progress dependent upon Federal funds?

Dr. **Temin**. I think that Federal funds have really been responsible for the majority of our progress up to now and will have to continue to be responsible; that we are dependent, either directly at the National Cancer Institute or being at the universities and supported by the National Cancer Institute in our research, requiring these things.

There is, as was said earlier by Dr. Fischinger, is good and increasing support of oncogene research. If we could be sure that we knew all the pieces of the puzzle, then I would say we would have at present time enough funding. Unfortunately, because we don't have all the pieces in the puzzle and we don't know where the answers are going to come from in biomedical research, we have to ask for continued increases in general support of biomedical research, because we found, even in these areas, that we think we can target research because we know all the answers, and then we find we really don't. And we're not yet at the place where we can say, "Let's put all our money on oncogenes," because, though we know now that oncogenes are going to be important in human cancer, in terms of breaking this trail from the altered oncogene to the phenotype, we don't know where in biology the important answers are going to come from and so we would ask for increased support of the whole range of biomedical research, knowing that important discoveries are going to come up, not where you expect them, but somewhere in this wide field.

I wish we could say you just do this and we'll give it to you. All we can say is——

Mrs. SCHNEIDER. So does the committee, I'm sure.

Dr. TEMIN. Yeah.

Mrs. SCHNEIDER. Well, I thank you very much. I regret that I do have to run off, but I hope that we will be able to continue this dialog at future opportunities. Thank you very much for your insights.

Dr. TEMIN. Thank you.

Mr. GORE. Thank you, surely.

Let me ask a few questions and then we're going to have to move on. This panel has been extremely interesting and I appreciate your statements.

Dr. Temin, as you know, the NIH, through its Recombinant Advisory Committee, or RAC, has established guidelines involving recombinant DNA experiments. Recently, questions about the safety of handling oncogenes and inserting them into bacteria have been raised in terms of potential effects on the health of lab workers. I understand that this is related to the level of containment required.

In your view, how much of a probability is there of accidentally transferring an oncogene to a lab worker or of it having an effect if it were to be transferred?

Dr. TEMIN. First, I want to say that we're not only regulated by the NIH regulations on working with recombinant DNA, but we're also regulated by NCI requirements for work with oncogenic viruses, so we work already under two levels of control. We believe these are completely adequate at the present time to prevent, in terms of our present knowledge, any possible harmful effect on workers.

What we have learned is that oncogenes don't simply change—one oncogene does not change a normal cell into a cancer cell, that you must have several changes so that having a single oncogene expressed in a bacteria will be much less dangerous than having that oncogene in a virus.

There have been no problems, medical problems, that I'm aware of in the last 70 years of work with these oncogenic viruses, and therefore, there is no reason to believe that taking the virus in another form, which is much less infectious, will have any more danger.

Mr. GORE. Uh-huh. So you don't think additional experimental evidence is necessary to satisfy doubts about accidental transfer?

Dr. TEMIN. No; the kind of experiments people are trying all the time—people have tried desperately to transform normal cells by transfection or injection of oncogenes, and all of the research has been that one oncogene cannot do it; you must set up very special circumstances to do that.

I don't think that further research is needed. Enough research has been published already relating to the safety issue.

Mr. GORE. Now, in laymen's terms, tell me why a—well, let me rephrase the question.

What you've just said about the virtual impossibility of an oncogene being mishandled in a laboratory causing cancer in a laboratory worker, can that explanation be used to describe why it is almost impossible for one individual to get cancer from another individual?

Dr. TEMIN. No.

Mr. GORE. All right.

Dr. TEMIN. OK. Cancer is a disease of an individual's body. Cancer in human—let me go—yeah, cancer in humans is a disease of one individual's body turning against itself——

Mr. GORE. Yes.

Dr. TEMIN [continuing]. All right, so that if I develop a cancer, it's my body attacking me. There's no way for my cancer to attack George because it's mine in the sense it's my body attacking myself. So that the cancer itself can only be transferred in animals under very special circumstances where you have no antibody reactions, essentially, where you set up a very special protected circumstance and so cancer of humans is never an infectious disease.

Mr. GORE. Uh-huh.

Dr. TEMIN. What is infectious is—in humans, like in the case of liver cancer, is the hepatitis B virus. The virus is infectious, but only a tenth of a percent of those who get the virus get the cancer——

Mr. GORE. Yeah.

Dr. TEMIN [continuing]. And the cancer is then not infectious.

Mr. GORE. Well, then, in a sense, the explanation is the same because in both cases, it is a multistep process which culminates in the individual's body——

Dr. TEMIN. In the individual's body——

Mr. GORE [continuing]. Attacking itself——

Dr. TEMIN [continuing]. That's right.

Mr. GORE [continuing]. But in instances where the triggering event is the intrusion of a virus——

Dr. TEMIN. Yes.

Mr. GORE [continuing]. To what extent—and this may be a hopelessly naive question—but to what extent in the future would you anticipate strategies to protect against those triggering viruses——

Dr. TEMIN. This is already started——

Mr. GORE. Yeah.

Dr. TEMIN. There are a million cases, new cases a year, of liver cancer and actually in Taiwan, this is an important problem, as it is in the People's Republic of China, and other less developed countries. It is confidently believed that the hepatitis B virus leads to this cancer by, as you indicated, a multistep process. There is now a vaccine which is manufactured by, Merck Sharp and Dohme and the Pasteur Institute against the hepatitis B virus. In China, they have started vaccine trials, taking a whole village, vaccinating one village, not vaccinating the next, and they're going to look in 20 years and see if there's an effect on liver cancer. So this is already started.

Mr. **Gore**. This was just reported in the Popular Press a week ago.

Dr. **Temin**. In the Popular Press was reported a second-generation vaccine. Now, the first-generation hepatitis B vaccine is made from the blood of people who have been infected by the virus——

Mr. **Gore**. I see.

Dr. **Temin**. The second-generation vaccine——

Mr. **Gore**. Is genetically engineered.

Dr. **Temin** [continuing]. Is genetically engineered, and this may be a cheaper vaccine to make.

Mr. **Gore**. Cheaper and more available.

How about an individual with an impaired immune system compromised——

Dr. **Temin**. If you're asking the question, if someone went about it and tried to make cancer in a person, could they do it, I would still guess that probably they couldn't, because these viruses don't—don't grow very easily in human cells; that there are multiple defenses in human beings, even with an impaired system—there are natural killer cells; there are other ways.

So that, given—if you ask, given the worst possible case of someone trying to do this, is it possible, I would say it may be possible, but it would be very, very difficult, and this would, of course, not be anything that would happen in normal laboratory practice, which, as I've indicated, is already regulated by both the recombinant DNA guidelines and also the guidelines for working with oncogenic viruses. So working under these guidelines, the answer would be, it is not possible.

Mr. **Gore**. OK. Now, others of you jump in if you see something that needs to be said. Let me again try to get an overview understanding of these mechanisms. You said that there are probably a limited number of specific——

Dr. **Temin**. Proto-oncogenes.

Mr. **Gore**. Yes; but beyond that, a specific number of pathways. You have translocation——

Dr. **Aaronson**. That's mechanism——

Mr. **Gore**. Mechanisms.

Dr. **Vande Woude**. Mechanisms by which they are activated.

Mr. **Gore**. OK. Now let me hone in on that, OK.

Are there probably a limited number of mechanisms by which oncogenes are activated?

Dr. **Temin**. Yes.

Mr. **Gore**. How many, roughly?

Dr. **Temin**. Ten.

Mr. **Gore**. Ten, roughly.

Dr. **Temin**. In a general sense, but I'm not sure that's a useful answer.

Mr. **Gore**. Well, tell me why not.

Dr. **Temin**. Well, because those are general classes of things. In other words, a translocation means moving from one chromosome to another. There can be many causes in the sense of different chemicals——

Mr. **Gore**. Yeah.

Dr. TEMIN [continuing]. Or different other things which can bring about a translocation.

Mr. GORE. OK, well, wait a minute, wait a minute. We've got the normal proto-oncogene——

Dr. TEMIN. Yes.

Mr. GORE [continuing]. And we know that it can be altered to become an oncogene.

Dr. TEMIN. Yes.

Mr. GORE. OK. There are approximately 10 ways that can happen.

Dr. TEMIN. Yes.

Mr. GORE. Are there two grand subdivisions, viral and environmental insult?

Dr. TEMIN. No, now that's——

Mr. GORE. Yeah.

Dr. TEMIN [continuing]. What the difficulty is. Both viruses and environmental insults cause these 10 ways of activation.

Mr. GORE. All 10.

Dr. TEMIN. All 10.

Mr. GORE. OK. All right.

OK, well, let's look at all of them. Did you want to add to that?

Dr. AARONSON. Not really.

Dr. TEMIN. I was a little over-simplifying, but I think it's——

Mr. GORE. OK. There may be some exceptions, is that right.

Dr. AARONSON. But even if there were 1,000——

Mr. GORE. Yeah.

Dr. AARONSON [continuing]. What we're trying to say is that the targets of all of those different mechanisms——

Mr. GORE. Yeah.

Dr. AARONSON [continuing]. Are these small set of genes, and therefore, the pathways leading to cancer may be relatively small.

Mr. GORE. That's the bottleneck. That's——

Dr. AARONSON. That's the bottom line in terms of—that's why we are somewhat optimistic——

Mr. GORE. Excited, yeah, I mean because you know that—that all of them have to go through that, but let's come back to the mechanisms, OK.

Now, if you had to divide the number of cases which result from virus, from the number of cases which result from environmental insult, do we have any way of doing that?

Dr. TEMIN. Yes; in people, we know that viruses are quite rare. In the United States, we know that viruses are essentially unimportant in the United States. OK.

Mr. GORE. Now, the viral mechanisms have assumed a more prominent place in our understanding of these mechanisms chiefly because it was through the understanding of retroviruses that the insight first occurred——

Dr. TEMIN. That's right.

Mr. GORE [continuing]. But in the United States, it is relatively rare for cancer to be actually triggered by a virus.

Dr. TEMIN. Yes.

Mr. GORE. OK?

Dr. TEMIN. Yes.

Mr. GORE. So in most cases, it is an environmental insult——

Dr. **Temin**. In the broad——

Mr. **Gore** [continuing]. That causes cancer. In the broadest sense of that, how would you define the phrase "environmental insult" in that broadest sense?

Dr. **Temin**. Well, in that broadest sense, the environmental insult involves things like smoking, other chemicals, radiation, but then we have to add what we call spontaneous mutation, which means we don't know what causes someone—some people think it's oxygen radicals. It's not known what leads to spontaneous mutation.

Dr. **Vande Woude**. There's also the inborne error of the system, which again excludes—it's not infallible. Every time the DNA's duplicated, there——

Mr. **Gore**. There's a certain given error rate.

Dr. **Vande Woude**. Right.

Dr. **Temin**. We're not sure whether—what the mechanism—that's what we call spontaneous mutation. It means we don't know what causes that.

And so, then there is, again, what we call lifestyles, where we don't know—we know, from epidemiology, that people who live in different ways, have different diets and so forth, have different——

Mr. **Gore**. Yeah.

Dr. **Temin** [continuing]. Incidences of specific cancers, and that we put in the category of environmental insult, but we don't know——

Mr. **Gore**. Yeah.

Dr. **Temin** [continuing]. Whether it's something they eat——

Mr. **Gore**. Sadness and stress.

Dr. **Temin**. Exactly.

Dr. **Vande Woude**. There are apt to be genetic factors. There are very likely to be genetic factors as well. Dr. Fischinger alluded to them earlier on, when he talked about heavy smokers. Only 20 percent of heavy smokers develop lung cancer; the other 80 percent do not, and what are the factors that regulate that?

Conceivably at some point, they could be identified——

Mr. **Gore**. Uh-huh.

Dr. **Vande Woude** [continuing]. And that would be a handle that we could utilize in predetermining.

Mr. **Gore**. OK, back to the 10 mechanisms. Do we have any way of determining which is most common among the 10?

Dr. **Temin**. Not yet but it's only in a fraction of cancers that we can find the altered proto-oncogenes. So Stuart used the idea about 20 percent and we think that there are of the order of three or four altered genes, so we only know of the order, then, of 5 percent of the total, so it—right now, we can't say that.

Mr. **Gore**. OK, what are the 10 mechanisms?

Dr. **Temin**. The 10 were on George's last slide——

Mr. **Gore**. I couldn't read them.

Dr. **Temin**. OK, translocation, meaning moving something from one chromosome to another——

Mr. **Gore**. Yeah. Now, what moves it?

Dr. **Temin**. It's not known, something that breaks DNA. Radiation is known to be able to cause translocations.

Mr. **Gore**. OK, next?

Dr. TEMIN. Next would be what Stuart mentioned in his next to last slide, was a base pair mutation, where a single base changes in the letters that make up the DNA, and this can be caused by chemicals—I guess most likely an alkalating agent—something like that. Also radiation——

Dr. AARONSON. Smoking.

Mr. GORE. Smoking does that?

Dr. TEMIN. So that would be a second mechanism.

A third mechanism is insertion of a promoter. This is where something moves in the gene and inserts a promoter.

A fourth——

Mr. GORE. A "promoter," that means that you produce more——

Dr. TEMIN. I'm sorry, controlling——

Mr. GORE [continuing]. Switch——

Dr. TEMIN. That's right, a switch, a switch, I'm sorry.

Mr. GORE. A switch. OK. All right, fine. Which is so you have——

Dr. TEMIN. More of it.

Mr. GORE. OK.

Dr. TEMIN. A fourth mechanism is duplication of the gene, so you have much more of the gene, and therefore, more of the product.

Mr. GORE. Uh-huh.

Dr. TEMIN. This occurs as a result of chemical treatment, things that poison cells so many chemotherapeutic agents lead to this gene over-duplication.

What were the others?

Mr. GORE. Yeah. Go ahead.

Dr. AARONSON. Those are the big——

Dr. TEMIN. Those are the major ones. Those are the major ones we know at the present time.

Mr. GORE. Do you think there are six others that are less significant?

Dr. VANDE WOUDE. Well, there's Wilm's tumor, which appears to be a deletion in a specific chromosome, and that's been pinpointed, as well as retinoblastoma is associated with losses of segments of chromosomes. The idea is that what remains is a recessive trait, but what remains then becomes dominant because of the loss of a normal counterpart of that gene. There are two copies of every gene in the cell.

There are other examples of that, perhaps, in certain kinds of leukemias that are associated with chromosomal abnormalities.

Mr. GORE. Uh-huh.

Dr. VANDE WOUDE. And those I alluded to that we can begin to pinpoint, knowing where breaks are, knowing from the gross optically microscopic anatomy of the chromosome where to begin looking, having probes to go in and identify those regions.

Mr. GORE. Uh-huh.

Dr. TEMIN. So that in retinoblastoma, they speak of chromosome loss being five; gene deletion, six; inactivating mutation, seven; inactivating insertion, either; and then I left two more for things that will be discovered.

So there're both the positive ones that we've mainly been talking about this morning and that we think there are also negative ones which we haven't discussed.

Mr. **Gore**. Uh-huh.

OK, that's very helpful. It's common in folk wisdom that a bereavement or a change in life situation that causes a change in attitude, can trigger the onset of cancer. Now that may be just mythology, but let me just ask you, can you tell me if you think that is mythology and if you don't, do you speculate on any kind of mechanism related to these discoveries that——

Dr. **Temin**. I don't want to answer that directly because I am just not sure, but I can—I want to use that to say that we have been talking essentially at a cellular level——

Mr. **Gore**. Yeah.

Dr. **Temin**. Now, a tumor is a mass of cells so that these cells, which are then altered by these genetic changes, have to grow in the body against all of the defenses of the body——

Mr. **Gore**. Uh-huh.

Dr. **Temin** [continuing]. And there is thought that things that you've been discussing, emotional factors, can influence the response of the body to the attempted growth of the tumor cells——

Mr. **Gore**. Uh-huh.

Dr. **Temin** [continuing]. And this may be the mechansim of such an effect if it exists. I'm not prepared to say whether it exists. Maybe my colleagues——

Dr. **Vande Woude**. I don't think so. It represents an area of research that we really can't even approach yet in a reasonable fashion to ask the right questions whether such system—mechanisms are possible.

Mr. **Gore**. Yeah, well, we know that attitude can affect the production of specific biochemical substances, so presumably that could suppress the body's ability to——

Dr. **Temin**. Defense mechanism.

Mr. **Gore**. Yeah.

Dr. **Temin**. In a broad—in a very broad sense, now, but when you think about that, the body—just as we speak of the body fighting an infectious disease, the body can, with its immunological mechanisms, fight the cancer.

Mr. **Gore**. All right.

Dr. Sherr, let me ask you a couple of questions. In those situations where a change in two proto-oncogenes is needed to initiate cancer, can both of the proto-oncogenes be affected by change in a single controlled gene?

Dr **Sherr**. It probably requires more than one mechanism. Since the genes are topologically distinct in this cell and are independently regulated, one would assume that if you're talking about hitting two genes, you really do need two independent hits.

Mr. **Gore**. OK. Can you speculate on how findings or techniques derived from oncogene studies might help us understand and treat other diseases such as immunological disorders, in addition to diabetes?

Dr. **Sherr**. Well, I'm not sure about immunological disorders. I think one of the—one of the interesting features of basic research in any field, certainly in this one, is that, as I indicated in my testimony, the payoffs may come in unexpected directions.

I think we have focused initially on a study of genes that we presumed to be determinants of cancer and, as we get some insight into the gene products, we realize that in some cases, the gene products have functions that are typical of receptors and that those receptors are general families of biological compounds which are important, not only in cancer, but in other illnesses as well.

Now, the insulin receptor and the receptor for insulinlike growth factors is very similar and probably the physiology of receptor signaling in general might tell us something about diabetes as well as about tumors.

Mr. **Gore**. OK.

Dr. **Sherr**. I think as far as receptors are concerned, the only other comment that I would make is I really think that we're just beginning to identify hormones for biological response modifiers that are very important in determining how cells communicate, and I would suspect that we really don't have a handle right now on the complete repertoire of such compounds.

Mr. **Gore**. OK.

Dr. Vande Woude, how much interaction is there between your organization and the National Cancer Institute in terms of setting research direction and following up on promising leads?

Dr. **Vande Woude**. Well, our program is really sponsored through contract by the National Cancer Institute and our program is strictly operated as a basic research program where we have full interaction between investigators in the cancer field and the environment for the basic research or the basic research environment is conducted under an academic environment, really.

Litton provides management capabilities for us, but the research is really done as any research organization in an academic environment would perform research.

Mr. **Gore**. All right, thank you.

Dr. Aaronson, you have pointed out that thanks to genetic engineering, we can identify oncogenes and acquire and purify their products. These products can then be examined to determine their structure and function in an attempt to develop inhibitors. These products are needed by the cell and malignancy is the result of runaway production of a normal product, or production of an altered product as a result of a mutation.

If you attempt to turn off the product, as you suggest, how would the cell be able to function without the particular product?

Dr. **Aaronson**. Well, the problem, of course, is to learn how to turn it off. I think that if that particular cell could be made to turn off the product that's bad, then we could live very well without that particular cell, which is a tumor cell. What you don't want to do, though, is turn off that gene or interfere with the normal product of all of the other cells of the body. You know—in other words, you want to hurt the tumor, but not hurt the normal cells, and your question's a good one, any modality that you would ever want to contemplate would have to take that consideration, you know, into the context of how you're going to approach things.

It's not easy, but we're not even at the place where we can, I think, genetically engineer a cell to turn off a particular gene.

Mr. **Gore**. OK. All right.

I have a lot of other questions, but we're running late on time, so we're going to have to move on to the next panel, but I want to thank all four of you for a fascinating presentation and I appreciate the manner in which you've coordinated your presentation and it's been very, very helpful to the committee.

I'd like to ask each witness to provide copies of the slides attached to testimony if that's at all possible so we can get those in the hearing record. I found them useful for understanding what you were presenting here and we'll give you any assistance necessary in copying those and making them available for the record.

But again, thank you all very much.

Dr. TEMIN. Thank you for listening to us and I also want to compliment you on your acuteness. I wish some of my graduate students asked questions like some of yours. [Laughter.]

Mr. GORE. Well, you're very kind. Thank you. Thank you for helping me understand this a little better.

Let me call now our third panel. Dr. Theodore Krontiris, professor of medicine at Tufts Medical School Cancer Research Center in Boston; and Stephen Turner, president of Oncor, Inc., in Gaithersburg, MD.

Dr. Krontiris, we will begin with you. Without objection, your entire prepared text will be included in the record. I said to the last panel, "give us the meat of it." Maybe if you could give us the carrots of it, in light of the subject——

Dr. KRONTIRIS. OK.

Mr. GORE [continuing]. If you could give us the substance of it, we'd appreciate it.

STATEMENTS OF DR. THEODORE G. KRONTIRIS, PROFESSOR OF MEDICINE, TUFTS MEDICAL SCHOOL CANCER RESEARCH CENTER, BOSTON, MA; AND STEPHEN C. TURNER, PRESIDENT, ONCOR, INC., GAITHERSBURG, MD

Dr. KRONTIRIS. OK, given the lateness of the hour and certainly the fact that many of my comments in the written record have been, I think, more than adequately covered by previous testimony, what I'll do is briefly make four points.

First of all, I want to reiterate——

Mr. GORE. Would you use those mikes, yeah, thank you.

Dr. KRONTIRIS [continuing]. I want to reiterate the warning that you stated at the outset of the subcommittee hearing. The reason for this is that we, all of know, that each time oncogene research surfaces and there's some public attention paid to it, given the certainly the excitement that scientists and clinicians feel, somehow a significant group of people get transmitted the idea that this—this research and these ideas will benefit them. That is not the case and it should be restated again and again.

Mr. GORE. It was your sensitivity and your statement at the beginning of your prepared testimony that led me to say that in my opening statement and I thank you for that.

Dr. KRONTIRIS. OK.

So the remainder of my talk, really, are the following three points: First of all, it's quite clear in the thread that's been running through previous testimony, but I think needs to be stated more overtly, that the oncogene research and what brings us here today is really the fusion of many different areas of basic research and certainly RNA tumor virus studies played a very prominent role in this and with it, however, were areas involving immunology and immunoglobulin genetics, recombinant DNA technology, investigators studying chromosome structure and particularly abnormalities of chromosome structure in cancer, that is, cytogenetics, individuals whose sole interest has been in transferring genes from one organism to another. We could go on and on. Cell biologists interested in cellular growth factors. All of these different areas have played distinct roles in what is now discussed as oncogene research.

Now, the significance of that is not merely a celebration, which I intend it to be, but also I think bears on what was raised a little earlier by Mr. Skeen, and that is, when someone in one particular area now makes a discovery, that discovery is immediately amplified and expanded upon in many different areas and it's quite a thing, I think, to behold among those involved in cancer research now. The extent to which discoveries in one area have reverberations in other areas. And with that, I think, given the extent to which there's an integration with biotechnology firms, these discoveries are, I think, with quite reasonable dispatch, exploited for any potential therapeutic benefit.

Now, the second part of this point is that many of the things that we have come up with today in the features of oncogene research that we've been discussing really come from very basic research. That is, scientists, following their noses in undirected programs primarily supported by the U.S. Government through the National Institutes of Health, and so now, at a time in which we are discussing the accelerated funding and targeting of funds to particular areas, which I think is certainly of some import. I think we ought to recognize the debt that we owe to these many scientists working on basic research.

Just to give you an example, as I recall, as a graduate student, reading a bunch of papers of molecular biologists who were in a very painstaking fashion dissecting the ways in which bacteria assembled and put their genetic information into certain forms so that it could be transmitted from bacterium into bacterium. At the same time, there were a number of individuals involved in trying to understand how pieces of DNA maintain themselves autonomously in bacteria. These pieces of DNA that we call plasma. This technology, which seemed of academic interest at the time, revolved into what we now call the recombinant DNA technology, so it just bears remembering.

Now, more to the point, the application of oncogene research to current cancer treatment, I think we've all heard of a number of potential applications which really sort of take the form, at least right now, of "Star Wars" cancer therapy. Really, some very, I think, important leads, but, as Dr. Aaronson has emphasized in a number of different occasions, certainly too early in the game to be able to say anything specific.

However, there is one aspect of this that I really would like to emphasize, which is that oncogene research is very likely to have an effect very much sooner than we think, not because we'll discover the magic bullet, but because it will allow us to apply much more rationally the therapies that we now have available, that is, the standard, routine surgery, chemotherapy and radiation therapy.

Now, what I mean by that specifically is that the impact of oncogene research will not be—I disagree that it will be first in the area of early disgnosis. That, I think, likely will not be the case. Where oncogene research will be applied—indeed, is being applied even now, is in the systematic class—better classification and staging of tumors. That's an area that's somewhat distinct from early disagnosis, although, obviously, early diagnosis has some role in that.

And these are two areas that are mentioned in my written text and that I want to emphasize, that clinicians have found to be very useful in trying to predict how groups of patients will behave. Again, it's a matter of statistics, but it's quite clear even now—and we saw a list of some 20 oncogenes, and there are more coming along the line—so many of them related to one another—that in trying to classify which oncogenes are involved in a particular patient's tumors, how the lesions arose, whether they're associated with chromosome abnormalities and maybe some of the other standard markers currently used for cancer, that this whole thing can be amalgamated into what would really be an imperical classification system, but which would have potential benefit in predicting how patients would respond to available modalities of treatment.

An example of that now is—again, alluding to the written statement—there are certain patients with a given kind of advanced carcinoma that some of whom respond very well to chemotherapy, but the chemotherapy is quite brutal, and those patients who don't respond to that chemotherapy actually have a significant dimunition of the quality of their remaining life. So I think that it's likely that oncogene research will fairly soon play some role in helping clinicians to make decisions as to—in which case to apply currently available therapies.

Finally, I want to just speak briefly about the issue of screening. That is my own particular area of interest and I think it bears on the issue of early diagnosis. I don't think there's any question that oncogene research will have, in a reasonable amount of time, some great benefit to confer on the area of early diagnosis, but the problem with early diagnosis will be then, as it is now, on whom to apply it. So, having a blood test or having a monoclonal antibody directed nuclear scan or having any of these sorts of technical facilities available will still lead you to the question of where do I use it. It's simply not feasible to take 225 million people and put them through these routines periodically to see if they have early pancreatic cancer. And I think it is there that the—perhaps one big help—obviously not exclusive aspect—will be trying to determine something about the genetic susceptibility of humans to cancer and I think that there are some very promising leads now with certain structural properties of DNA that are called RFLP's, and I think that it's already been demonstrated that they are of some use in some very rare cancers that have been alluded to previously: Wilm's tumor and retinoblastoma, but I think it is quite likely, and I think we'll know within several years that that general approach, certainly a beginning, but a very general approach may be applied to more—I want to say "more important tumors," but to more prevalent tumors.

I think I'll conclude my testimony.

[The prepared statement of Dr. Krontiris follows:]

PREPARED STATEMENT OF THEODORE G. KRONTIRIS, M.S., PH.D., NEW ENGLAND MEDICAL CENTER AND TUFTS UNIVERSITY SCHOOL OF MEDICINE

I've been asked to describe the potential clinical application of oncogene research in the areas of cancer diagnosis, treatment and individual risk prediction. It should be clear at the outset that the work that I'll be discussing is not likely to benefit those people who are now seriously ill with cancer. Obviously those people who have cancer which is now amenable to standard modalities of therapy can expect effective treatment. However, those people with advanced, difficult cases or with types of cancer for which no treatment is satisfactory should not expect that the approaches mentioned here will apply to them. No one wants to be responsible for adding false hope to the burdens of cancer patients and their families.

With this caution stated, we can still relate that cancer clinicians and basic scientists are quite excited by the therapeutic possibilities offered by oncogene research. The exuberance exists because, for the first time, the ways we envision dealing with cancer are directed by some understanding of the underlying mechanisms. Although our understanding is far from complete, we all expect that our future efforts will be guided by a more precise knowledge of how cancer arises and progresses.

Diagnosis

New ideas and new technology must be measured against existing approaches. It seems certain that oncogene research will contribute methods by which pathologists may determine the existence of cancer in biopsies more confidently. This is obviously important, not only in terms of treating the right people, but perhaps also in treating them earlier. Researchers both here at the National Cancer Institute and at Stanford University have already demonstrated in one subset of cancer, malignant lymphoma, that diagnostic precision can be heightened by the application of current knowledge. In the case of the Stanford group, the technique they applied allowed them to detect lymphoma among certain cardiac-transplant recipients in which the diagnosis had previously been uncertain. Since our ability to detect inappropriate oncogene expression and abnormal oncogene products is quite sensitive, this methodology will be useful, and useful soon, in making the diagnosis in marginal cases.

There are several other important issues in the area of cancer diagnosis. The first of these, which I have just alluded to, is the possibility of early detection. We will continue to accumulate specific probes which identify oncogenes and pinpoint where they are being expressed. The likelihood is, then, that current detection techniques, such as cytology and scanning, will be amalgamated with these probes. The result will be a powerful amplification of current methods. While the technology of early detection will almost certainly improve over the next several years, the basic problem of cancer screening remains: that is, how can we identify populations in which it will be cost-effective to apply expensive, if powerful, screening methods. I cannot exclude the possibility that a variety of cheap and sensitive techniques will be developed; but the likelihood is that they will be expensive and sensitive. Therefore, we will need to find ways of identifying people for whom screening is likely to be of great benefit. I'll have more to say about this in a moment.

Two final aspects of cancer diagnosis are the related subjects of classification and staging. Beyond our requirements of knowing whether something is cancer and whether the cancer is at an early stage is the additional necessity of determining tumor subtypes and the extent of disease progression. These areas have traditionally been important for clinicians because in many types of cancer, oncologists can use the information to make predictions about how a particular tumor is likely to behave--for example, how the tumor is likely to respond to available therapy. Classification and staging must be made more accurate and extended to all types of cancer. It is in this area that I feel oncogene research will have its most immediate impact. By correlating tumor behavior with specific oncogenes, the lesions that activate them, particular chromosome abnormalities and more traditional tumor markers, a comprehensive system of classification can be generated. The importance of this is that, even before any new, specific therapies are derived from oncogene work, we may hope for a more rational application of existing therapies. For example, in certain types of cancer, subgroups of affected patients will respond very well to chemotherapy. However, the chemotherapy is often extremely aggressive and extremely toxic. Those patients who do not respond suffer adversely in the quality of remaining life. What clinicians need to know, and what oncogene research may provide, is an accurate prediction of which patients will respond. In this way, one spares the other patients the toxicity and potential life-threatening complications of chemotherapy.

Therapy

How cancer research will affect cancer therapy and how soon the benefits will be appreciated are the most difficult subjects to discuss. Although there are several obvious possibilities, these must be viewed in the context of other therapeutic strategies which are not directly related to oncogene research. In this fashion we get a broader perspective on potential applications of oncogene research to treatment and on the interdependence of current approaches.

Cancer therapy is now divided into three general areas--surgery, chemotherapy, and radiation therapy. In cases of cancer which are not amenable to surgery, chemotherapy and radiation therapy are often applied. These approaches are non-specific; that is, they kill growing cells whether the growing cells are cancerous or normal. Therefore, treatments are toxic and sometimes life-threatening. In addition, many kinds of tumors are naturally resistant to the currently available therapies. This is why cancer researchers have always sought to understand the mechanisms which underlie the generation of malignant cells. It is hoped that therapy might then be designed which would be more effective in killing tumor cells and more specific in sparing normal tissue. It is for just this reason, namely, that oncogene research promises to uncover the mechanisms by which tumors arise, that we hold such great hope for the clinical application of this research to cancer therapy.

The direct effect of research on therapy will be the rational design of agents which counteract the effects of abnormal oncogene products. Research in this area is still at a very basic level. As we have heard, the identification of these products and their localization in cells are the current focus of intense investigation. Some progress is being made in determining how they act within the cell under normal circumstances and how the disruption of this normal function results in the uncontrolled proliferation we call cancer. Therefore, we can envision the general direction which therapeutic interventions might take, but specific details await further research. In my opinion, one of the most exciting recent discoveries is that lower organisms, particularly yeast, possess genes very much related to human oncogenes. This finding suggests that this class of genes has been very highly conserved thoughout evolution to serve a specific function in cellular metabolism and growth control. It has recently been demonstrated by a number of groups that the yeast genes may be replaced by abnormal human genes. Since yeast are a lot easier to manipulate in test tubes than are human beings, they offer great potential for understanding how a certain number of oncogenes work and how they may be counteracted. This particular system is probably not going to find general application. Nevertheless, an important class of human oncogenes may be understood and subverted by this approach.

Oncogene research may have indirect benefits by its influence on two other distinct therapeutic strategies currently being investigated. The first of these is a collection of methods directed at modulating the immune system of patients to help them fight cancer with their own natural defense mechanisms. Some of the basic recombinant DNA technology and gene transfer methodology have been, and will continue to be, useful in dissecting the immune system. Perhaps we can then isolate and activate those components of the immune system which will be most effective in helping the patient's body overcome a tumor.

The second approach, just now underway, is called "differentiation" therapy. Most scientists feel that there is a relationship between how mature a cell is, that is, how much of its resources are committed to specialized functions, and how much the cell proliferates. The more mature the cell is, the less likely it is to divide. Injury and, of course, cancer may upset this relationship. However, certain agents have been described which apparently cause cells to mature, or differentiate. Since oncogene expression is linked to cell proliferation, perhaps our knowledge of oncogenes may be used to monitor the effectiveness of such drugs and to help design them, as well.

Risk Prediction

The aim of work on individual risk prediction is to answer affirmatively the following questions:

(1) In a family with defined hereditary susceptibility to cancer, can we predict which individuals in that family are most likely to acquire the disease?

(2) In the general population is it possible to identity individuals at high risk for developing cancer, taking into account the influence of environmental hazards?

(3) In a group of individuals, all of whom have the same kind of cancer at the same stage of advancement, can we predict how each individual's genetic background will affect the course of his disease?

The attempts at answering these questions are just now beginning. This work is based on the usefulness of certain structural properties of genes which are called restriction fragment length polymorphisms (RFLPs). Several years ago investigators at MIT, the University of Massachusetts, the University of Utah and Stanford University jointly described the means by which RFLPs might be employed in human genetic studies. Since that time, with information provided by the molecular cloning of oncogenes, several observations have been made which suggest that understanding the genetic basis of cancer susceptibility may be possible. Presently the strongest data come from the study of a group of very rare hereditary cancers. A number of research groups have been active in showing that the RFLP approach is likely to be helpful in predicting individual susceptibility to these cancers. Our hope is, however, that the approach may be generalized to encompass common tumors, as well.

I mentioned previously that an important problem in cancer screening is the specification of subpopulations in which cost-effective screening may be conducted. A scientific basis for assigning risk will greatly facilitate the process of screening, even if the results of genetic studies are subject to a wide margin of error. For example, we can expect that most individuals who will be identified as having genes which make them susceptible to cancer will not actually develop the disease. This is because multiple factors, both environmental and genetic, are likely to be involved. Nevertheless, before we possess complete comprehension of factors which govern genetic risk, even fragmentary knowledge will assist us in identifying people for whom screening will discover cancer at an early stage.

Conclusions

What precise form future cancer therapy may take is not uppermost in our minds. Most of us, I suspect, are interested primarily in the question, "When?" I think I gave some notion of timing in my opening remarks: People now ill with untreatable cancer will not benefit. Furthermore, we should bear in mind that the time scale really has two components. The first component is how long it takes us to prove that something is possible. The second is the time it takes us to accomplish what we know we can do. In the area of risk prediction for example, one or two years will be required before we will know whether the current approaches will be productive. However, it will then take several more years to collect the data actually required to make accurate risk statements. In the area of cancer diagnosis, we already know that useful application is possible. Correspondingly, the time to achieving that benefit will be short-- within the next few years. The final and most important category, therapy, is the most difficult to predict. Although we have every reason to be hopeful that definitive results will occur within a decade, it is not possible to provide a closer estimate. Nevertheless, we should take comfort in the fact that oncogene research will certainly lead to the more effective, and more humane, application of currently available treatments.

BIOGRAPHICAL INFORMATION

Theodore G. Krontiris, M.D., Ph.D.

Graduated from the Albert Einstein College of Medicine, Bronx, New York, in 1977. Internship and Residencies in Internal Medicine at the Brigham and Women's Hospital, Boston, Mass., 1977-1981. Postdoctoral research training at the Dana-Farber Cancer Institute, Boston, 1978-1982. Assistant Professor of Medicine (Hematology-Oncology), New England Medical Center and Staff Scientist, Cancer Research Center, Tufts University School of Medicine, Boston, 1982-present. Assistant Professor of Molecular Biology and Microbiology, Tufts University School of Medicine, 1984. Major research interest: the genetics of cancer susceptibility.

Mr. **Gore**. Thank you, thank you, excellent statement and I appreciate it.

I'll hold off on questions until we hear from Mr. Turner. Stephen C. Turner is president of Oncor, Inc., in Gaithersburg, MD, and we appreciate you joining us, particularly on short notice, Mr. Turner. You have a unique perspective on the commercialization of techniques and products arising out of this exciting new field and we're delighted to have you here and please proceed.

Mr. **Turner**. Thank you very much, and I do apologize for the lack of a prepared transcript for the record, but I did get my invitation yesterday afternoon, so——

Mr. **Gore**. We appreciate you filling in on short notice when another witness canceled and we're glad to have you here.

Mr. **Turner**. If it's all right, I'll do a little bit of reading and please feel free to interrupt me if anything piques your interest that you'd like to pursue further. I'll keep my comments fairly brief.

The commercialization of oncogene technology actually began in March of this year when a 1-year-old American company, Oncor, actually began shipping DNA probes that are used today for the detection of human oncogenes. These products, inside of only 3 months, have been sold into 300 labs. Half of these are outside of the United States. I'm trying to make the point that commercialization actually is beginning to be spawned.

What I would like to address very quickly is the subject of how markets and businesses are going to develop in this most promising technology. As founder and president of a small company, all of my working hours are spent working on the questions of transitioning into a business the very technology that you have heard so adequately described here today.

The enormity of the cancer problem—I think you have all the statistics you need. Suffice it to say that the average American's cumulative risk of having cancer through age of 74 is about 26 percent. It's a pretty high number.

Mr. **Gore**. To put that in perspective, we were jotting down some figures up here. Today is the 40th anniversary of D-day; 135,000 troops landed with 10,000 casualties. If there were 125,000 survivors, about 30,000 of them will contract cancer, according to the normal statistical rate, and about 15,000, or more than perished during the D-day landing, will or already have died as a result of cancer. Just to underscore your point about the enormity of the challenge.

Mr. **Turner**. That's a very chilling way of putting it.

For all the money that's been spent, I think it's fair to say, from a consumer's point of view, that the relative weakness of our current technology for the finding and the treatment of cancer is reflected in these types of statistics. They haven't changed a whole lot.

Existing diagnostics for cancer today are dominated by scanning techniques, which I won't go into, but are dependent upon the visualization of tumors. This represents a—catching a tumor at a fairly advanced stage and, as has been mentioned, limits the effectiveness of any treatment that's going to be provided at that point.

Oncogene technology, as you have heard, will lead to detecting very early, very formative molecular events leading to the development of the tumor, thus, allowing diagnosis at a far earlier point than waiting until one can visualize the actual disease. Eventually, hopefully, this means you can catch these events prior to the patient even knowing he's sick or presenting any symptoms.

I happen to believe that you will see a revolution take place in the next decade in the way tumors are classified and diagnosed and that actually a redefining will take place of what we call these malignancies which up to now have been primarily classified microscopically through their morphology.

That, then—the increase in precision, I believe, will lead to the development of new, more powerful classes of therapies being delivered to the diagnosis. It's a chicken-and-egg problem; the more precise the classification of the tumors can be made, which is going to be one of the early commercializations of oncogene technology, the more precisely then one can look at therapeutic activities and hopefully commercialize those.

Business development will parallel the technology, of course, and as this is a promising but very embryonic technology, you will generally see a number of new companies, such as mine, being spawned and dedicated to it. Over the next couple of years, I think there will be announcements of technical discoveries, but relatively little in the marketplace.

Companies like Oncor, I think, will be very busy simplifying the technology, learning how to produce these products in large scale, and, of course, satisfying the requirements of the FDA to register these products for clinical use.

You have to keep in mind that when we sell a product today, it's to maybe 1 of 1,000 labs in the world that could use it, and to use it today takes about 10 to 13 days, very highly skilled people, a lot of other expenses.

The role of the company is obviously to take that and reduce it down to a single day into something that a lower skilled person can run, and that's, of course, a natural job for business.

This type of debugging and problem-solving will take place in industry in parallel with the questions that remain to be answered in the research environment at the same time. Beginning around 1986, I think you will see the use of oncogene technology in the classification of tumors, as was mentioned, and I think later in this decade, the technology will be used broadly in a variety of direct diagnosis of cancer.

My projections are that there will be an international market approaching $1 billion by 1992 and growing relatively fast. During this decade, there'll be parallel pharmaceutical activity, as I mentioned, and these, with their longer leadtimes, should start hitting the market around that time.

Finally, and I'm the first to acknowledge that this is only in the dream stage, a decade from now, the technology may allow us to identify asymptomatic individuals who have activated oncogenes or who are presenting gene products, and this, of course, is an exciting thing.

At very early ages, we could screen to identify our population those individuals with higher potential risks for specific cancers.

They have an oncogene; they have a gene product, but there is no other events, and that the research would have been done to associate these molecular events with long-term risk of development of specific tumors.

I think it's when we get into those points that the country will have finally begun to get its arms around the cancer dilemma.

Industry will be developing at many levels from my dedicated startup company to the major pharmaceutical companies, and it will take all of our talents to provide the vision and the capital to commercialize what this country's outstanding life science research establishment is currently discovering.

To conclude very quickly, the industry is going to be very competitive and it will be competitive on an international basis, as Europe and Japan will also vie for leadership. We have had instances where labs and companies have—from other countries—have actually called us and attempted to procure our entire production capability at this point. Technology transfer is rapid in this business and is a concern.

So you are seeing here today the very first steps in the creation of a mini-industry. I think it's important for the United States to lead in this and the other new technologies that will come before you, and as one who's committed to this, I believe we can do so.

I would like to suggest that, if possible, we maintain the present favorable environment for long-term capital gains. We maintain the country's commitment to its life science research, which is the envy of the world, and we do allow industry and academic teams to combine in commercial ventures when both parties see merit.

I would also suggest that the FDA consider fast-tracking diagnostic applications that are pioneering oncogene technology as I'm sure other countries will be doing this.

Thank you.

Mr. GORE. Well, thank you very much. I appreciate that testimony. Very, very helpful.

Dr. Krontiris, in your paper in the New England Journal of Medicine, you indicated that oncogene research will aid oncologists in three ways: One, enhance tumor diagnosis; two, simple, noninvasive risk prediction methods; and three, more effective therapeutic methods.

I'd like to ask you about risk prediction, or the ability to establish that an individual has greater susceptibility to a particular disease. First of all, what do you think cancer susceptibility is related to, in addition to oncogenes? The basic genetic makeup, environmental factors, stress? What do you think about that?

Dr. KRONTIRIS. Well, I think there are two components, at least, that immediately come to mind. First of all, I think that it will eventually be shown, simply by looking hard enough, that certain people already have abnormal oncogenes, if not as blatant as the ones that we're discovering now in tumors, at least ones that whose level of function would be enough over a lifetime to generate a slightly larger risk so that when these other independent events that Dr. Temin referred to occur, that person is just a little bit more susceptible than someone else.

The other, more major, I think—the determinant of susceptibility, at least on a genetic basis, at least right now, is that certain people deal with environmental toxins in different ways than others, and so, for example, in dealing with aromatic hydrocarbons of certain enzymes, more active in some people than others, that may lead either to detoxifying or to changing these things into their more proximal carcinogen forms. Such people you might expect to be, let's say, more susceptible to cigarette smoke than others.

I don't think we know the answer to that yet, but certainly it's an even bet that of those people who develop cancer because they smoke cigarettes, they'll fall into both of those groups. My betting would be more in the latter group than the former, at least right now.

Mr. GORE. Well, do you foresee a time when blood tests will tell people about their enhanced susceptibility and lead to some sort of counseling?

Dr. KRONTIRIS. Yes, yes. I think probably in the short term, even within 5 years, the number of the, let's say, these particular enzymes that I refer to, one can envision developing tests from simple sputum samples, for example, that would tell you whether or not someone would be more susceptible, and then you could use that to help coax people to stop smoking.

Mr. GORE. How far away would you think we are from that?

Dr. KRONTIRIS. I don't like to put a number on it. I'd say, certainly, in those particular aspects, perhaps over the next 5 years. They're not technically very difficult. It will involve identifying more and more such systems, but they don't represent the kind of conceptual breakthroughs, for example, that we're talking about, have discussed earlier.

Mr. GORE. Uh-huh, uh-huh.

We already have a number of laboratory procedures which appear to offer help for diagnosis and therapy. Do you have any opinion as to which will bloom into clinical reality first?

Dr. KRONTIRIS. Could you give me an example?

Mr. GORE. The Dutch example that I was——

Dr. KRONTIRIS. Yes.

Mr. GORE [continuing]. Discussing earlier is the Georgetown—excuse me——

Dr. KRONTIRIS. Right.

Mr. GORE [contuining]. The Freel technique.

Dr. KRONTIRIS. Well, certainly, that particular finding and in general——

Mr. GORE. Feller technique, I'm sorry, excuse me.

Dr. KRONTIRIS [continuing]. In general diagnostic methods based on monoclonal antibodies are promising. There's still a lot to go through in terms of actually collecting the numbers to be able to say something in some statistically relevant fashion.

It'll be a while. I would say several years, certainly, before even that method as a general approach will be validated.

Mr. GORE. Well, Mr. Turner, I bet you've given some thought to this. Which would you predict will be earliest to come to clinical reality?

Mr. TURNER. I have the advantage of not having the first presentations, so——

Mr. GORE. OK. [Laughter.]

Mr. **Turner**. I may not answer in an accurate manner.

To me, it's a form of evolution and the first things out will not be the biggest, but they will be things that fill holes in the marketplace where you can quickly deliver a new technology. The need is great enough that people will put up with a high degree of expense or difficulties of getting the products and they will generally be unexciting when viewed from a global cancer-curing sort of thing.

They're of interest to business because that's where we do the real work and the real ground-building to launch the second- and third-generation applications of the technology. That's why I generally was pushing kind of a 10-year timeframe.

Now, keep in mind that at least today, there are two kinds of products when we talk about products for oncogene detection. One is the antibodies which detect a product of the genes or protein and the other are the nucleic acid or, today, DNA probes, which are actual hybridized copies of segments of the genes or the genes themselves that are used to detect the existence of a oncogene in a tumor cell. Those are two very different types of products.

The antibodies, of course, have been around a long time; it's a technology we're more familiar with. It's logical that those should seep into the marketplace more quickly. DNA technology, while in my view may be ultimately more promising, has a great deal of work to be done to make it into a convenient, reliable product system.

However, my own feeling was that in the next 2 or 3 years, the first places these products would come into the clinical environment would be to enhance the classification of tumors which are difficult to tell apart today. So if you have tumor A and tumor B and they look under the microscope the same and, therefore, for practical bases, you can't prescribe therapy differently for this, then the oncologist, the clinical oncologist, would like and would pay for a oncogene probe or an oncogene antibody that would allow him to differentiate these two forms of tumor cells which then would allow him to differentiate the therapy and then, of course, monitor the course of the therapy.

It's that diagnosis-splitting, I think, that's first going to hit, and then I think, looking out 5 years, you'll see more direct diagnosis. If this oncogene is activated, this cancer is present; if this oncogene product is circulating, the same idea, and that, over the next 5 or 10 years. This is speculation, but I'm happy to state what I've sorted out.

Mr. **Gore**. All right. It sounds to me like you've got a pretty level-headed approach to it. Do you plan to do in-house research or would you use an approach involving the funding of academic scientists already active in the field in your development of these systems to simplify the research techniques?

Mr. **Turner**. It's a good and important question. It's a blend. Whether you're a small company or a large company, I think the answer is the same. In the initial stages, of course, the capital of the company is very dear. You have in-house research and my company certainly does, but you allocate it to the highest priority, which is usually relative to getting a product in a form that it can be used on a reliable basis and so we say "research," but it's really quality control, making the product very reliable.

You can imagine the problem if we were to offer something like this and for it not to do exactly what we say it's going to do. So for the—what you might call "technical direction," answering questions like what ought the company to work on, what should it be targeting in the way of its product engineering activities. For this, we go to outside consultants. If the outside consultant has a specific expertise, we will actually put money into a university lab which my company has done in two cases and let that person do the research in the academic lab and then the company negotiates rights and royalty arrangements with the universities.

I happen to favor these arrangements, particularly in the early stages, when you don't want to go through heavy duplication of capital investment to duplicate what's already out there in many academic labs.

Mr. GORE. All right, very good. Do you think that training programs for clinical laboratory personnel should be upgraded to enhance their ability to use the techniques of molecular biology?

Mr. TURNER. Definitely. It's already happening, but anything that can be done to get the medtech level person in some way familiar with the handling of molecular biology is a definite plus.

Mr. GORE. Is there any society or organization attempting to do this or capable of doing it?

Mr. TURNER. I'm sure there are some. I can't put my finger on one right offhand, but I want to emphasize that these things have a way of happening and I've been to meetings and—particularly I'm thinking of the hematologists and the oncologists—they're aggressive, professional groups. They read the New England Journal of Medicine, which today is full of molecular biology articles. A few years ago, you never saw those things, and there seems to be, at the very least, heightened awareness of the need to make sure their people have these skills.

Mr. GORE. Well, very good. I want to thank both of you for finishing out a very interesting, and I hope productive hearing. I want to thank all of our witnesses who have testified today. The subcommittee will be continuing its effort to monitor the exciting new developments in this field in its consideration with the full committee of the biomedical research budget, we want to give the proper attention to the developments which are taking place here, and I want to thank all of you for participating in the hearing today. And with that, we'll stand adjourned.

[Whereupon, at 1 p.m., the subcommittee was adjourned, to reconvene subject to the call of the Chair.]

APPENDIX

McARDLE LABORATORY
FOR CANCER RESEARCH
DEPARTMENT OF ONCOLOGY
MEDICAL SCHOOL, UNIVERSITY OF WISCONSIN

June 8, 1984

Congressman Albert Gore, Jr.
Committee on Science and Technology
U.S. House of Representatives
Suite 2321 Rayburn House Office Building
Washington, D.C. 20515

Dear Representative Gore:

I appreciated your interest and attention at the hearings on Wednesday, June 6. I especially admired your flare for colorful analogies.

I want to clarify one point which may have been left a little obscure. There are three sets of numbers to be considered in oncogenesis. One is the number of potential oncogenes, perhaps forty. Second is the number of ways to change them into active oncogenes and the number of active oncogenes required for neoplasia. There are perhaps four positive and four negative ways known for activation now and some small, three to five say, mutations needed. And finally there is the question of how many pathways are involved in the neoplastic process. What Dr. Aaronson was suggesting was that in spite of the large number of potential oncogenes and different ways of activating them, that they may all involve a small number of pathways. For example, these may be one pathway that controls cell division, another that controls cell immortality, and another that controls cell metastasis.

Under this way of thinking, then the tasks of therapy would just be involved in protecting those three pathways.

I hope this clarifys things. Please contact me if I can be of further assistance.

With best regards,

Sincerely yours,

Howard M Temin

Howard M. Temin
American Cancer Society, Rusch,
and Steenbock Professor

HMT:mjg

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